# PHOSPHORUS CONTAINING DENDRIMERS: SURFACE CHEMISTRY AND APPLICATIONS

Final Technical Report

by

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United States Army

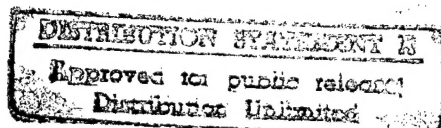EUROPEAN RESEARCH OFFICE OF THE U.S. ARMY

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FERROUS SCRAP IS NOT A CRITICAL MATERIAL -- IMPORTANT, YES; ESSENTIAL YES; SIGNIFICANT, YES; BUT NOT CRITICAL. I SAY THAT NOT TO MINIMIZE THE IMPORTANCE OF SCRAP AS A MAJOR RAW MATERIAL IN IRON AND STEELMAKING. RATHER, SCRAP IS IN SUCH ABUNDANCE THROUGHOUT OUR NATION, AND IS SO READILY AVAILABLE IN SUCH QUANTITIES THAT NOTHING SO UBIQUITOUS CAN BE CRITICAL BY DEFINITION. THE CRITICAL FACT OF SCRAP IRON IS ITS NEED FOR A MARKET.

SCRAP IS AVAILABLE TO BE MADE INTO NEW STEEL, BUT THERE ARE FEW USES FOR SCRAP OTHER THAN TO BE RECYCLED INTO THAT NEW IRON AND STEEL. THUS, SCRAP IS NOT A CRITICAL MATERIAL BUT A MARKET IS CRITICAL FOR THAT MATERIAL.

THE OPPORTUNITIES TO EXPAND THE RECOVERY OF IRON AND STEEL DISCARDS ARE TREMENDOUS AS ARE THE BENEFITS OF SUCH EXPANSION, AND BOTH WILL BE REALIZED WHEN IRON AND STEEL-MAKERS INCREASE THEIR DEMAND FOR SCRAP TO CHARGE THEIR MELTING FURNACES.

THE RESERVOIR OF IRON AND STEEL DISCARDS IN THE UNITED STATE IS ENORMOUS -- HUNDREDS OF MILLIONS OF TONS OF MAT-ERIAL THAT WILL BECOME EITHER AN ASSET OR A LIABILITY TO OUR ECONOMY -- THAT REPRESENT AN INCREDIBLE CONSERVATION POTEN-TIAL OR A CONSERVATION DISASTER -- DEPENDING ON THE CHOICE MADE FOR METALLICS IN FUTURE STEELMAKING.

IF WE ARE NOT ABLE TO RECOVER THESE METALLIC UNITS FOR RECYCLING INTO NEW PRODUCTS, BY DEFAULT THEY BECOME BOTH AN ECONOMIC AND SOCIAL LIABILITY TO THE JURISDICTIONS IN WHICH THEY ARE LOCATED. WHEN VACANT CITY LOTS AND COUNTRY ROADSIDES BECOME THE DUMPING GROUNDS FOR DERELICT AUTOMOBILES, UNWANTED REFRIGERATORS AND THE LIKE, CITIZENS GENERALLY DEMAND ACTION BY THEIR LOCAL GOVERNMENT TO "GET RID OF THE JUNK." THE RESULT IS AN EXPENDITURE OF TAX DOLLARS TO DIS-POSE OF WHAT COULD BE, BUT BY CHOICE IS NOT, AN INDUSTRIAL RAW MATERIAL.

THE ROLE FOR OBSOLETE SCRAP BEGINS WITH THE COLLECTOR, WHO TRANSPORTS IT TO THE SCRAP PLANT FOR PROCESSING AND THEN SHIPMENT AS A PREPARED PRODUCT TO STEEL MILLS AND FOUNDRIES. IN THIS SCENERIO, SCRAP IS TRANSFORMED INTO AN ECONOMIC AND ENVIRONMENTAL ASSET. CERTAINLY IT MAKES MORE SENSE IF SCRAP CAN BE HANDLED THROUGH THE PRIVATE SECTOR GENERATING JOBS, MAKING EXPENDITURES FOR GOODS AND SERVICES, EARNING PROFITS, AND PAYING TAX REVENUES, RATHER THAN BEING A DRAIN ON OUR TAX DOLLARS WHEN IT IS MERELY DISPOSED OF, NOT RECYCLED. HOW COULD ANYONE DISAGREE.

BUT IN REGARD TO THE TOPIC FOR THIS MORNING, IN ADDITION TO CONSERVING ONE AND ONE HALF MILLION TONS OF IRON ORE, EPA FOUND THAT WHEN ONE MILLION TONS OF SCRAP IRON ARE USED TO MAKE NEW STEEL, AIR POLLUTION EFFLUENTS ARE REDUCED 86 PERCENT -- 208 MILLION POUNDS; WATER POLLUTION IS REDUCED 76 PERCENT

## Summary

The synthesis of phosphorus containing dendrimers is described up to the fifth generation (96 terminal groups). The surface chemistry of these dendrimers allows the grafting of various functionalities such as phosphate (6 $O-P(O)(OEt)_2$ groups), aminophosphate (up to 96 $N-P(O)(OEt)_2$ groups), aminophosphite (up to 96 $N-P(OEt)_2$ groups), functionalized phosphonate (up to 96 $HC(OH)P(O)(OR)_2$ ($R$ = Et, $(CH_2)_{11}CH_3$), up to 96 $HC(N-Pr)P(O)(OEt)_2$, or up to 48 $CH=CH-P(O)(OEt)_2$), phosphorus ylide (6 $C(O)CH=P(Ph)_3$), carboxylic acid (up to 24 $CH=CH-C(O)OH$), and tetraazamacrocycle (up to 12 cyclam). These surface fuctionalities have been chosen due to the wellknown properties of the corresponding monomers and/or polymers in various areas such as adhesives, flame retardants, fuel additives, sequestring agents...

## Key words

# Table of Contents

## List of Appendixes:

List of Participating Scientific Personnel

Publications issued from this report:

    I - Phosphate, phosphite, ylide and phosphonate terminated dendrimers
    Prévôté, D.; Caminade, A.M.; Majoral, J.P. *J. Org. Chem.* (in press).

    II - Application of the Horner-Wadsworth-Emmons reaction to the functionalization of
dendrimers: Synthesis of amino acid terminated dendrimers
    Prévôté, D.; Le Roy-Gourvenec, S.; Caminade, A.M.; Masson, S.; Majoral, J.P.
*Synthesis* (accepted).

# A - Introduction

Dendrimers[1] constitute a new class of macromolecules whose size, shape, and molecular weight are rigorously controled. Furthermore, their highly branched structure which induce the formation of internal voids and the occurence of all the reactive functions on the surface make dendrimers unique among polymers.
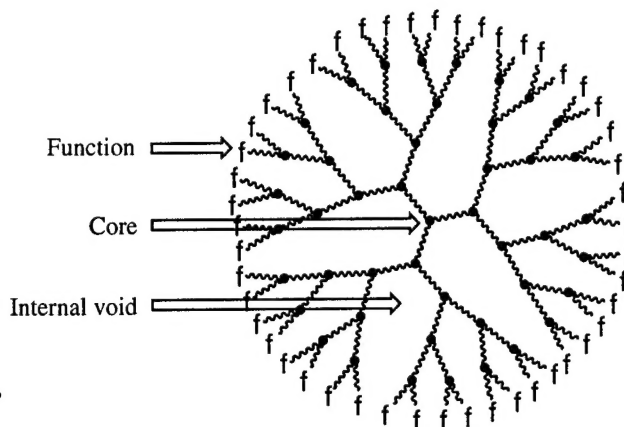


**Fourth Generation of a Dendrimer**

The synthesis of organic dendrimers and silicon containing dendrimers are well explored areas, which now come out to the study of properties and applications of these compounds. Concerning phosphorus containing dendrimers, the expertise of our research group is unrivalled in the world (60% of all the papers ever published to date in this field come from our group)[2]. The methods of synthesis of phosphorus containing dendrimers we have developed present several significant advantages: cheap industrially available starting materials, quantitative yields, possibility to check easily the construction of the dendrimer by $^{31}$P NMR, solubility in several common organic solvents, and stability towards hydrolysis and bases.

The objectives of the present study was to take advantage of the large number of reactive functions located on the surface of dendrimers to graft various new functional groups susceptible to bring properties in several fields, mainly adhesives, flame retardant, additives, or sequestring agents. For this purpose, we have tried to graft several types of phosphorus containing groups such as phosphates, aminophosphates, aminophosphites, phosphorus ylides, with emphasis on functionalized phosphonates, whose properties of the monomers and/or corresponding polymers are well known in most of the fields evoked above, and in many other fields. The grafting of carboxylic acids and tetraazamacrocycles should also induce properties in the field of adhesives and sequestring agents.
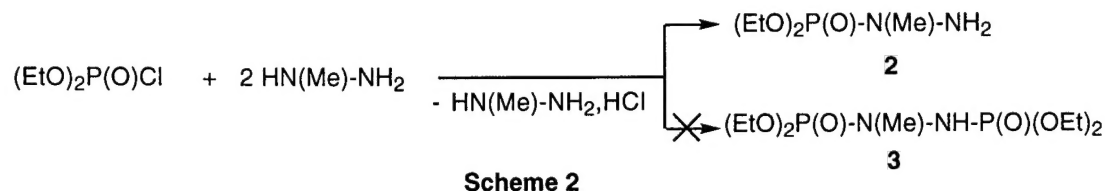
The present report describes only fruitful experiments. All unsuccessful attempts which have been included in the four interim reports are not included in this final report. All the dendrimers described have been isolated and fully characterized by NMR ($^{31}$P, $^1$H, and $^{13}$C), IR, elmental analyses, in some cases by mass spectrometry, and by X-ray diffraction for a small molecule.

# B - Results

## I - Synthesis of dendrimers

Dendrimers from generation 0 to generation 5 were prepared by the repetition of a two steps procedure: nucleophilic substitution of chlorine by hydroxybenzaldehyde, and Schiff condensation reaction (Scheme 1, Table 1, Figure 1).

$$S=PCl_3 + 3\ NaO\!-\!\langle\ \rangle\!-\!CHO \xrightarrow[-3\ NaCl]{} S=P\!\left(O\!-\!\langle\ \rangle\!-\!CHO\right)_3$$

**1-[G'₀]**

$$S=P\!\left(O\!-\!\langle\ \rangle\!-\!CHO\right)_3 + 3\ H_2N\!-\!N\!-\!\overset{Me}{\underset{S}{P}}\!\overset{Cl}{Cl} \xrightarrow[-3\ H_2O]{} S=P\!\left(O\!-\!\langle\ \rangle\!-\!C=N\!-\!N\!-\!\overset{Me}{\underset{S}{P}}\!\overset{Cl}{Cl}\right)_3$$

**1-[G'₀]**                **1-[G₁]**

$$1\text{-}[G_1] + 6\ NaO\!-\!\langle\ \rangle\!-\!CHO \longrightarrow S=P\!\left(O\!-\!\langle\ \rangle\!-\!C=N\!-\!N\!-\!P\!\begin{smallmatrix}O\!-\!\langle\ \rangle\!-\!CHO\\ O\!-\!\langle\ \rangle\!-\!CHO\end{smallmatrix}\right)_3$$

**1-[G'₁]**

$$\equiv Dend\!\left(\!C=O\atop H\right)_y \quad (y=6)$$

$$\longrightarrow\ \longrightarrow\ \longrightarrow\ 1\text{-}[G'_5]$$

$$\equiv Dend\!\left(\!C=O\atop H\right)_y \quad (y=96)$$

**Scheme 1**

| Generation n = | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| (Cl) | **1-[G₁]** | **1-[G₂]** | **1-[G₃]** | **1-[G₄]** | **1-[G₅]** |
| Number (CHO) | **1-[G'₁]** | **1-[G'₂]** | **1-[G'₃]** | **1-[G'₄]** | **1-[G'₅]** |
| Number of Cl or CHO | 6 | 12 | 24 | 48 | 96 |
| Molecular weight (terminal Cl) | 909 | 2389 | 5349 | 11269 | 23108 |
| Molecular weight (terminal CHO) | 1423 | 3417 | 7405 | 15381 | 31331 |

***Table 1**: Some characteristic data concerning dendrimers **1-[G₁] –1-[G₅]** (terminal P-Cl bonds) and **1-[G'₁] –1-[G'₅]** (terminal CHO groups).*
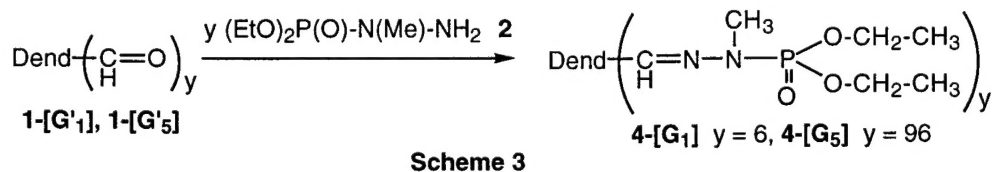
## II - Anchorage of phosphorus groups

### II - 1 - Anchorage of aminophosphate groups

The strategy investigated for the grafting of aminophosphate groups consists of the reaction of dendrimers $1-[G'_1]$ and $1-[G'_5]$ (generations 1 and 5, respectively) with a new phospho monohydrazide $2$ (Scheme 3). Compound $2$ is prepared by reacting the chlorophosphonate $(EtO)_2P(O)Cl$ with methylhydrazine (Scheme 2).
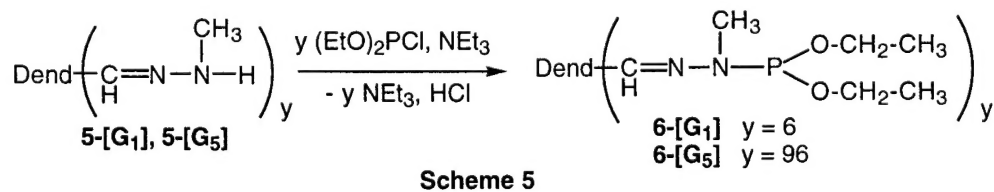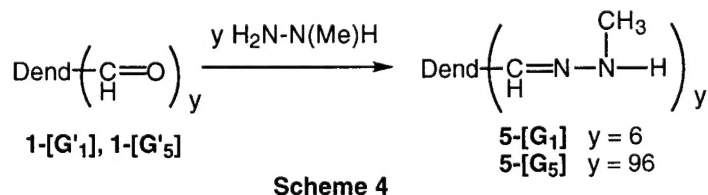
$(EtO)_2P(O)Cl$  +  $2\ HN(Me)-NH_2$ $\xrightarrow{- HN(Me)-NH_2,HCl}$

→ $(EtO)_2P(O)-N(Me)-NH_2$

**2**

$\times$→ $(EtO)_2P(O)-N(Me)-NH-P(O)(OEt)_2$

**3**

**Scheme 2**

The reaction of formation of $2$ is performed at low temperature (-80°C) to avoid the formation of a by-product such as $3$ which can be formed via condensation of $2$ with $(EtO)_2P(O)Cl$.

$Dend\left(\!\!\begin{array}{c}C=O\\H\end{array}\!\!\right)_y$ $\xrightarrow{y\ (EtO)_2P(O)-N(Me)-NH_2\ \ \mathbf{2}}$ $Dend\left(\!\!\begin{array}{c}CH_3\\|\\C=N-N-P\overset{O-CH_2-CH_3}{\underset{O-CH_2-CH_3}{\diagdown}}\\H\ \ \ \ \ \|\\O\end{array}\!\!\right)_y$

$1-[G'_1], 1-[G'_5]$

$4-[G_1]\ y = 6,\ 4-[G_5]\ y = 96$

**Scheme 3**

The new dendrimers $4-[G_1]$ and $4-[G_5]$ possessing 6 or 96 terminal aminophosphate groups respectively are obtained as white powders (Figure 1).

### II - 2 - Anchorage of aminophosphite groups

Grafting of aminophosphite groups was successfully performed by reacting dendrimers $5-[G_1]$ and $5-[G_5]$ possessing 6 and 96 terminal $N(CH_3)H$ groups respectively with the chlorophosphite $(EtO)_2PCl$ (Scheme 5, Figure 1). Arborols $5-[G_1]$ and $5-[G_5]$ were easily prepared by reacting $1-[G'_1]$ and $1-[G'_5]$ with methylhydrazine (Scheme 4).

$Dend\left(\!\!\begin{array}{c}C=O\\H\end{array}\!\!\right)_y$ $\xrightarrow{y\ H_2N-N(Me)H}$ $Dend\left(\!\!\begin{array}{c}CH_3\\|\\C=N-N-H\\H\end{array}\!\!\right)_y$

$1-[G'_1], 1-[G'_5]$

$5-[G_1]\ \ y = 6$
$5-[G_5]\ \ y = 96$

**Scheme 4**

$Dend\left(\!\!\begin{array}{c}CH_3\\|\\C=N-N-H\\H\end{array}\!\!\right)_y$ $\xrightarrow[- y\ NEt_3,\ HCl]{y\ (EtO)_2PCl,\ NEt_3}$ $Dend\left(\!\!\begin{array}{c}CH_3\\|\\C=N-N-P\overset{O-CH_2-CH_3}{\underset{O-CH_2-CH_3}{\diagdown}}\\H\end{array}\!\!\right)_y$

$5-[G_1], 5-[G_5]$

$6-[G_1]\ \ y = 6$
$6-[G_5]\ \ y = 96$

**Scheme 5**

Dendrimers $6-[G_1]$ and $6-[G_5]$ are sensitive to hydrolysis and oxidation. Cleavage of the terminal nitrogen-phosphorus bond allows to recover $5-[G_1]$ and $5-[G_5]$ with the formation of $(EtO)_2P(O)H$.
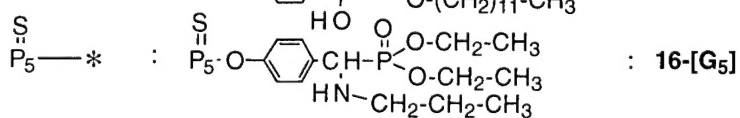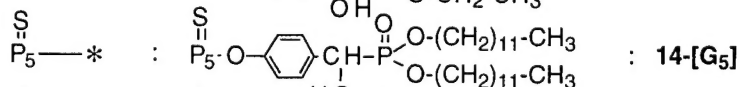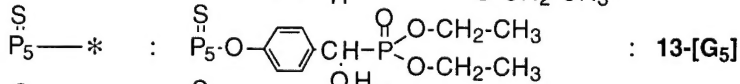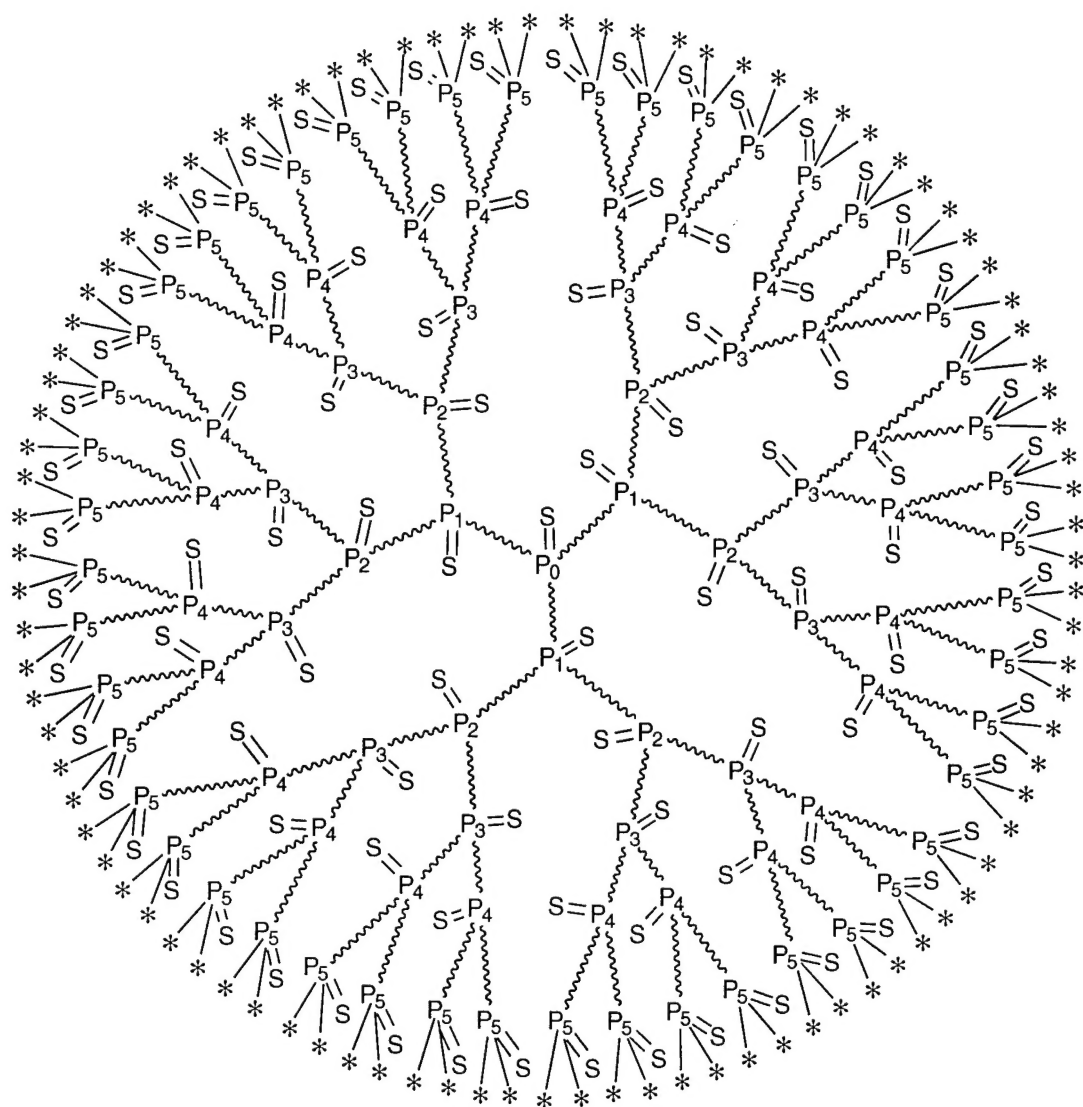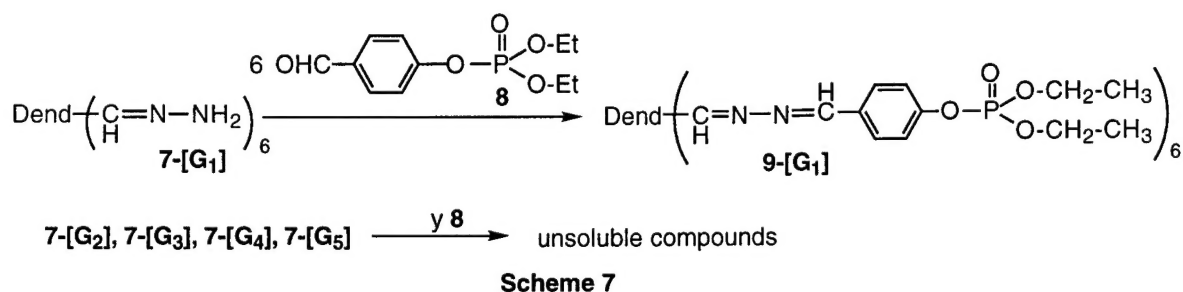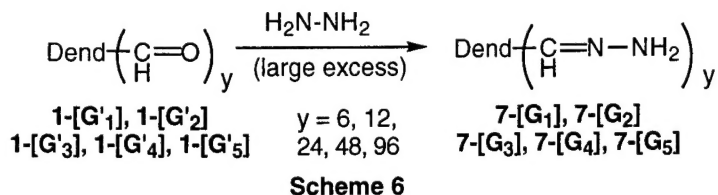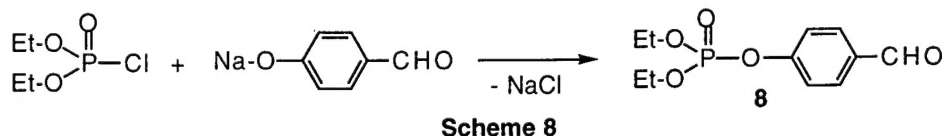
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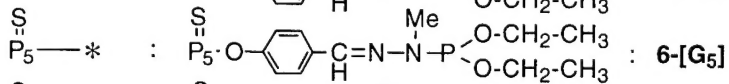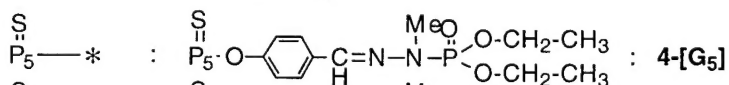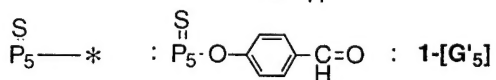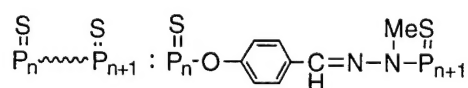


Figure 1

*II - 3 - Anchorage of phosphate groups*

The formation of a dendrimer possessing terminal phosphate groups involves

i) the preparation of dendrimers having terminal $NH_2$ groups $7\text{-}[G_1]$ - $7\text{-}[G_5]$ (Scheme 6)

ii) the synthesis of a new ligand $(EtO)_2P(O)OC_6H_4CHO$ **8** (Scheme 8)

iii) the reaction of $7\text{-}[G_1]$ - $7\text{-}[G_5]$ with **8** to give dendrimers $9\text{-}[G_1]$ - $9\text{-}[G_5]$ (Scheme 7).



$$\text{Dend}\!\left(\!\begin{array}{c}C=O\\H\end{array}\!\right)_y \xrightarrow[\text{(large excess)}]{H_2N\text{-}NH_2} \text{Dend}\!\left(\!\begin{array}{c}C=N-NH_2\\H\end{array}\!\right)_y$$

**1-[G'$_1$], 1-[G'$_2$]**          y = 6, 12,          **7-[G$_1$], 7-[G$_2$]**
**1-[G'$_3$], 1-[G'$_4$], 1-[G'$_5$]**     24, 48, 96     **7-[G$_3$], 7-[G$_4$], 7-[G$_5$]**

**Scheme 6**



$7\text{-}[G_2], 7\text{-}[G_3], 7\text{-}[G_4], 7\text{-}[G_5] \xrightarrow{\text{y } 8}$ unsoluble compounds

**Scheme 7**

Derivative **8** is prepared as follows:



**Scheme 8**

The dendrimer $9\text{-}[G_1]$ (72% yield) incorporates six terminal phosphate groups. Unfortunately the reaction of $1\text{-}[G'_5]$ with 96 equivalents of **8** affords insoluble material. Therefore, such a condensation reaction was attempted with **8** and dendrimers of generation 2 ($7\text{-}[G_2]$) 3 ($7\text{-}[G_3]$) or 4 ($7\text{-}[G_4]$). In all cases insoluble powders were obtained and characterizations were not possible.

It appears that the introduction in the framework of the molecule of CH=N-N=CH sequences dramatically reduces the solubility of the resulting products preventing from rigorous characterization.
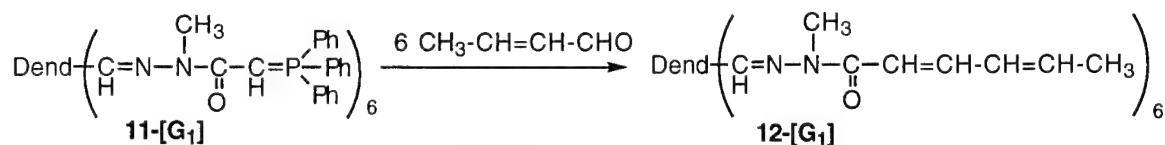
*II - 4 - Anchorage of phosphorus ylide groups*

Addition of terminal NH groups of the dendrimer $5\text{-}[G_1]$ on the carbon carbon double bond of the cumulene $Ph_3P=C=C=O$ **10** was undertaken (Scheme 9).



**Scheme 9**
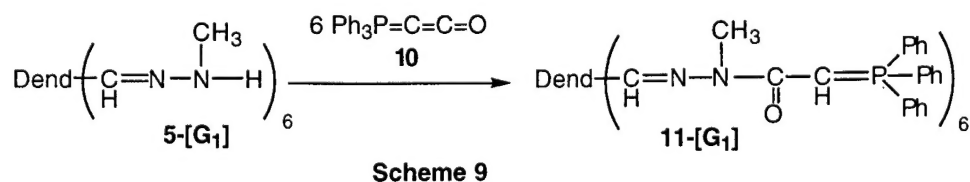
Temptative extension of this type of reaction to higher generations ($5\text{-}[G_2]$, $5\text{-}[G_3]$) led only to unsoluble materials.

Terminal ylide groups of **11-[G₁]** remain very reactive. For example, a Wittig reaction can be performed by reacting **11-[G₁]** with crotonaldehyde CH₃CH=CH-CHO affording dendrimer **12-[G₁]** (Scheme 10).

$$\text{Dend}\left(\begin{array}{c}\text{CH}_3\\ |\\ \text{C=N}-\text{N}-\text{C}-\text{C=P}-\text{Ph}\\ \text{H}\quad\;\; \| \;\; \text{H}\;\text{Ph}\\ \text{O}\end{array}\right)_6 \xrightarrow{\text{6 CH}_3\text{-CH=CH-CHO}} \text{Dend}\left(\begin{array}{c}\text{CH}_3\\ |\\ \text{C=N}-\text{N}-\text{C}-\text{CH=CH-CH=CH-CH}_3\\ \text{H}\quad\;\; \|\\ \text{O}\end{array}\right)_6$$

**11-[G₁]**  　　　　　　　　　　　　　　　　　**12-[G₁]**

**Scheme 10**

*II - 5 - Anchorage of phosphonate groups*

　　II - 5 - a - Addition to terminal aldehyde groups

Several tries were performed to graft in good yields phosphonate groups on the terminal aldehyde groups (Scheme 11, Figure 1).

$$\text{Dend}\left(\begin{array}{c}\text{C=O}\\ \text{H}\end{array}\right)_y \xrightarrow[\text{(excess)}]{\text{H-P(O)(OEt)}_2} \text{Dend}\left(\begin{array}{c}\text{O}\diagdown{}^{\text{H}}\quad\text{O}\\ | \quad\quad \|\quad\diagup\text{O-CH}_2\text{-CH}_3\\ \text{C}-\!-\!-\text{P}\\ \text{H}\quad\quad\quad\diagdown\text{O-CH}_2\text{-CH}_3\end{array}\right)_y$$

**1-[G′₁], 1-[G′₂]**　　　　　y = 6, 12,　　　　**13-[G₁], 13-[G₂]**
**1-[G′₃], 1-[G′₄], 1-[G′₅]**　　24, 48, 96　　**13-[G₃], 13-[G₄], 13-[G₅]**
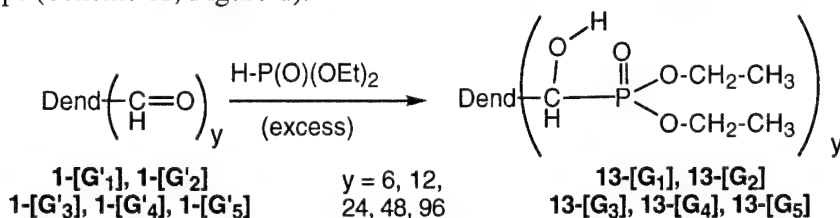
**Scheme 11**

This type of reaction was done in several conditions. After several attempts, the best method was the following one: the dendrimer was dissolved in a mixture of [(EtO)₂P(O)H, NEt₃], at room temperature, the phosphonate acting as reagent and solvent. This experiment gave the best results and allowed us to graft from 6 to 96 phosphonates groups (see Table 2).
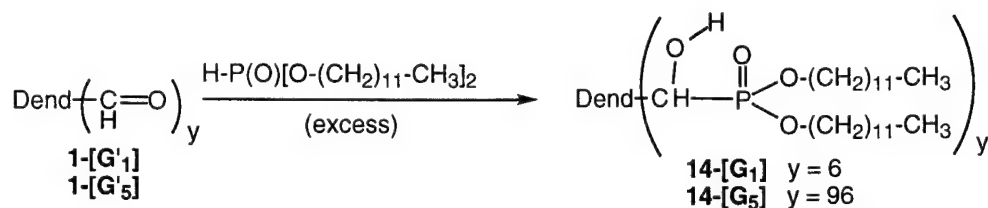
| Generation n = | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Compound | **13-[G₁]** | **13-[G₂]** | **13-[G₃]** | **13-[G₄]** | **13-[G₅]** |
| Number of terminal phosphonate groups -CH(OH)-P(O)(OEt)₂ | 6 | 12 | 24 | 48 | 96 |
| Molecular weight | 2252 | 5074 | 10719 | 22010 | 44589 |

**Table 2:** *Characteristic data concerning dendrimers with -CH(OH)-P(O)(OEt)₂ terminal groups.*

It should be mentioned the interest of this reaction which leads to phosphonate end groups but also to secondary alcohols end groups which should be of help for adhesive properties.

The same type of addition reaction was performed with another phosphonate $(C_{12}H_{25}O)_2P(O)H$ to avoid problems of solubility encountered with $(EtO)_2P(O)H$: compound with 96 $CH(OH)$-$P(O)(OEt)_2$ groups start to be poorly soluble in common organic solvents and NMR data were collected in $CD_3OD$.

The grafting of $(C_{12}H_{25}O)_2P(O)$ groups was undertaken on dendrimers $1$-$[G'_1]$ and $1$-$[G'_5]$ (Table 3) in the same experimental conditions than that used with $(C_2H_5O)_2P(O)H$ and afforded compounds now easily soluble in $CH_2Cl_2$ or $CHCl_3$ (Scheme 12, Figure 1).

Dend$\left(\begin{array}{c} C=O \\ H \end{array}\right)_y$  $\xrightarrow[\text{(excess)}]{\text{H-P(O)[O-(CH}_2)_{11}\text{-CH}_3]_2}$  Dend$\left(\begin{array}{c} CH-P \\ \end{array}\right)_y$

1-[G'$_1$]
1-[G'$_5$]

14-[G$_1$]  y = 6
14-[G$_5$]  y = 96

**Scheme 12**

| Generation n = | 1 | 5 |
|---|---|---|
| Compound number | **14-[G$_1$]** | **14-[G$_5$]** |
| Number of terminal phosphonate groups CH(OH)-P(O)(OC$_{12}$H$_{25}$)$_2$ | 6 | 96 |
| Molecular weight | 3935 | 7152 |

***Table 3***: *Dendrimers with terminal CH(OH)-P(O)(OC$_{12}$H$_{25}$)$_2$ groups*

### II - 5 - b - Addition to terminal imino groups

New dendrimers with terminal imino groups were prepared as follows (Scheme 13):

Dend$\left(\begin{array}{c} C=O \\ H \end{array}\right)_y$ + y H$_2$NCH$_2$CH$_2$CH$_3$ $\longrightarrow$ Dend$\left(\begin{array}{c} C=NCH_2CH_2CH_3 \\ H \end{array}\right)_y$

1-[G'$_1$]
1-[G'$_5$]

15-[G$_1$]  y = 6
15-[G$_5$]  y = 96
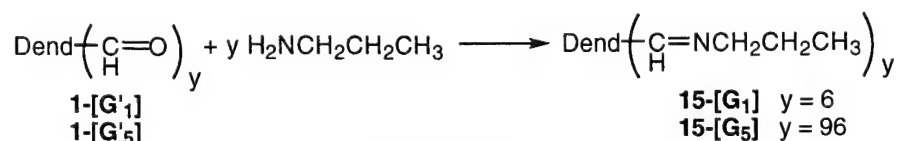
**Scheme 13**

Dendrimers $15$-$[G_1]$ and $15$-$[G_5]$ possessing 6 or 96 terminal imino groups respectively were further reacted with $(EtO)_2P(O)H$ again used as solvent. This reaction allowed to obtain new dendrimers $16$-$[G_1]$ and $16$-$[G_5]$ arising from oxidative addition of the P-H bond on imine functions (Scheme 14, Table 4, Figure 1).
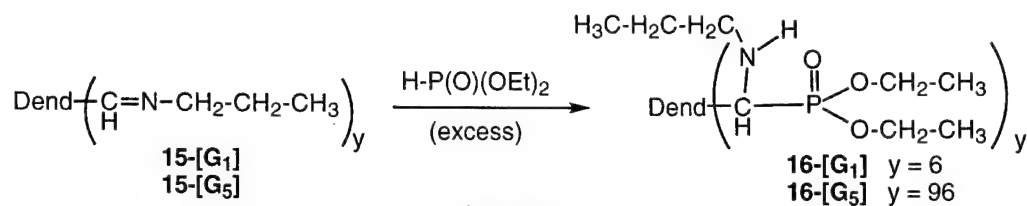
**Scheme 14**

| Generation n = | 1 | 5 |
|---|---|---|
| Compound number | **16-[G₁]** | **16-[G₅]** |
| Number of terminal phosphonate groups -CH(NHC₃H₇)-P(O)(OC₂H₅)₂ | 6 | 96 |
| Molecular weight | 2498 | 48535 |

*Table 4*: Dendrimers with terminal -CH(NHC$_3$H$_7$)-P(O)(OC$_2$H$_5$)$_2$ groups

### II - 5 - c - Horner-Wadsworth-Emmons reaction on terminal aldehyde groups

Vinylphosphonates moieties (from 6 to 48 units) were grafted on the surface of phosphorus containing dendrimers according to the reactions indicated in scheme 15.
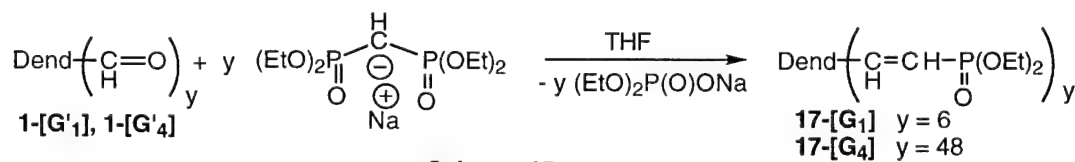


**Scheme 15**

The reaction consists of the generation of the carbanionic species [[(EtO)$_2$P(O)]$_2$CH]⁻ which is further reacted with terminal aldehyde groups. The reaction proceeded in very mild conditions and allowed to obtain new dendrimers **17-[G₁]** and **17-[G₄]** as white powders.

## III - Acid terminated dendrimers

After several unsuccessful attempts to graft phosphorus acids such as P(O)(OH)$_2$ groups on the surface of dendrimers, we turned our efforts to the synthesis of dendrimers possessing carboxylic acid chain ends.

The strategy used, outlined in scheme 16, is also a Horner-Wadsworth-Emmons reaction.

y (EtO)$_2$P(O)CH$_2$-COOH



**Scheme 16**

1-[G'$_1$]  y = 6
1-[G'$_3$]  y = 24

18-[G$_1$]  y = 6
18-[G$_3$]  y = 24
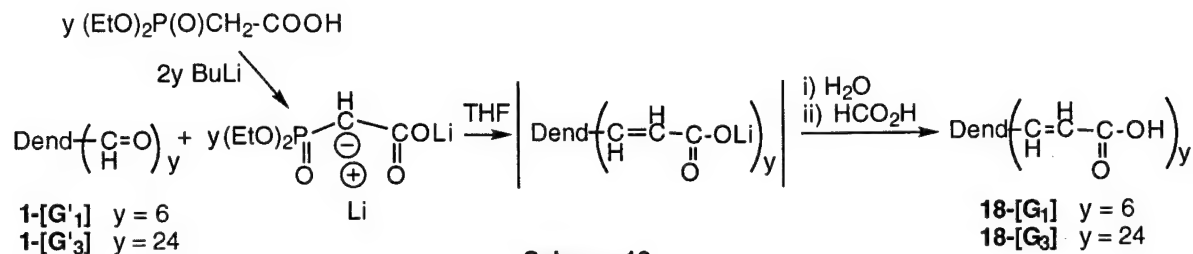
Reactions proceed nicely and give first the CH=CHC(O)OLi derivatives (soluble in water, but not isolated), then the new acidic terminated macromolecules **18-[G$_1$]** and **18-[G$_3$]** possessing six or 24 terminal CO$_2$H groups, which are isolated after treatment with formic acid. It is noteworthy that only the trans isomers are obtained.

## IV - Grafting of tetraazamacrocycles

We planed to prepare new dendrimers possessing both phosphorus groups and nitrogen macrocycles with the aim to have strong useful ligands able to bring new properties due to the presence of various groups on phosphorus and free NH groups.

In order to find the good experimental conditions for reactions involving P(S)Cl$_2$ end groups of dendrimers, we reacted first the monomer **19** with macrocycles **20**, **22** and **24** (Schemes 17 and 18). In a typical experiment a dichloromethane solution of **19** (1 equiv.) 1,4,8,11-tetraazacyclotetradecane **20** (cyclam, 1 equiv) and potassium carbonate (2 equiv.) was stirred for 4 days at room temperature. After workup the macrocycle **21** was isolated in 55% yield (Scheme 17).
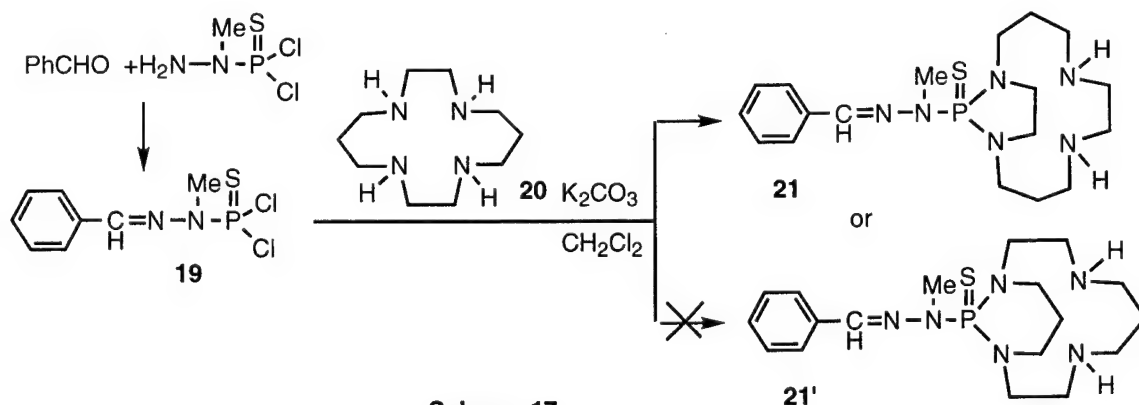


**Scheme 17**

$^1$H and $^{13}$C NMR data appeared in agreement with the proposed structure and seemed to rule out the form **21'** in which a diazaphosphorinane unit (six membered ring) is created.

Similarly the treatment of **19** with 1,4,8,11-tetraazacyclopentadecane **22** in the same experimental conditions led to the macrocyclic species **23** or **23'** (Scheme 18). In this case $^1$H and $^{13}$C NMR did not allow us to choose between forms **23** and **23'** but allowed to exclude form **23"**. On the other hand **19** reacted unequivocally with 1,4,8,11-tetraazacyclotetradecane -5,7 dione **24** to give the macrocycle **25** characterized by X-ray diffraction (see Figure 2).
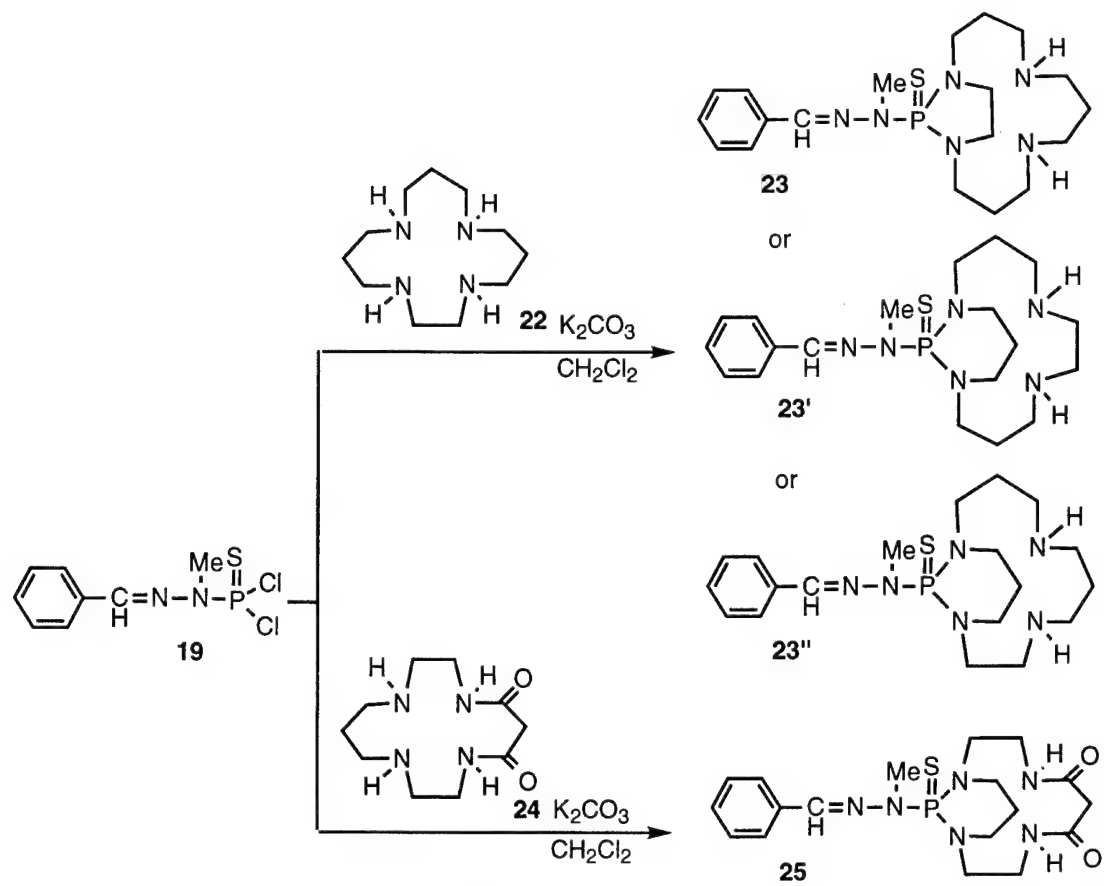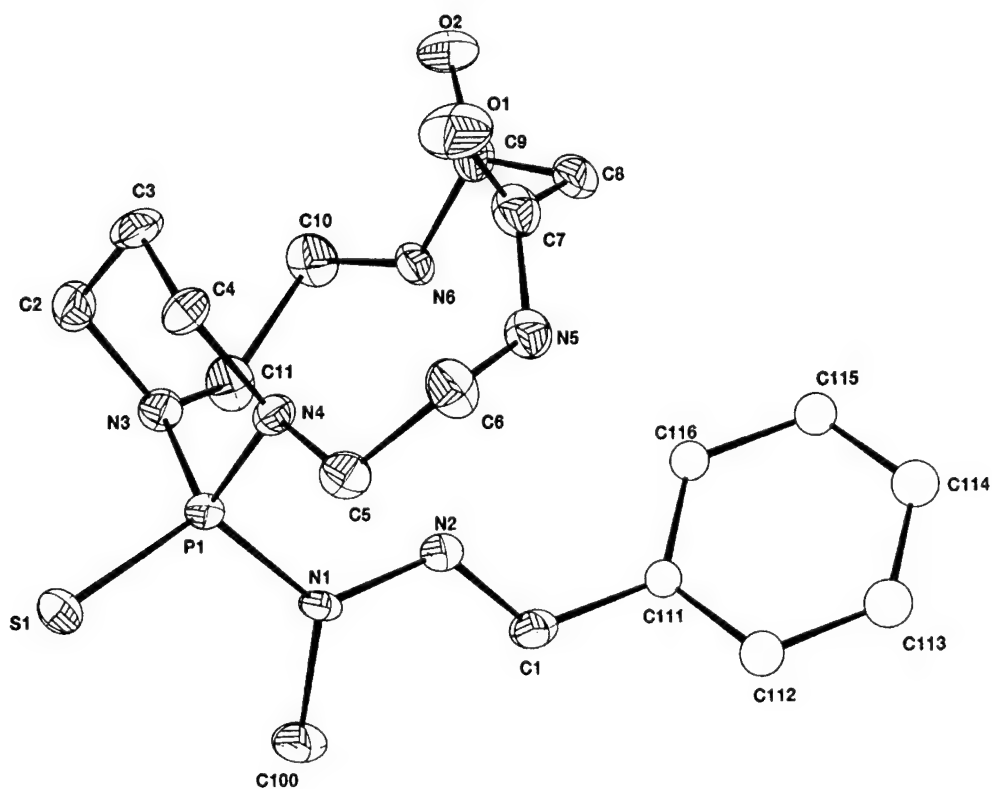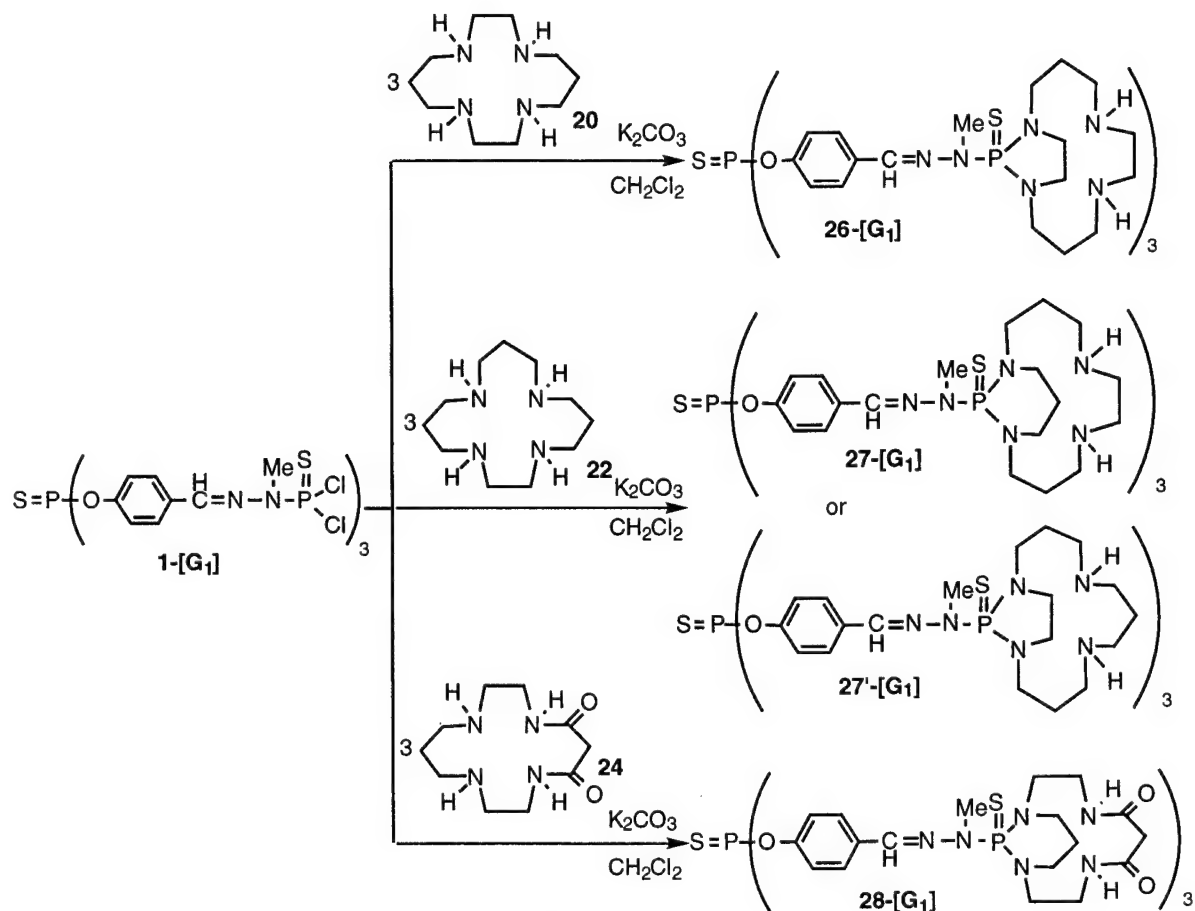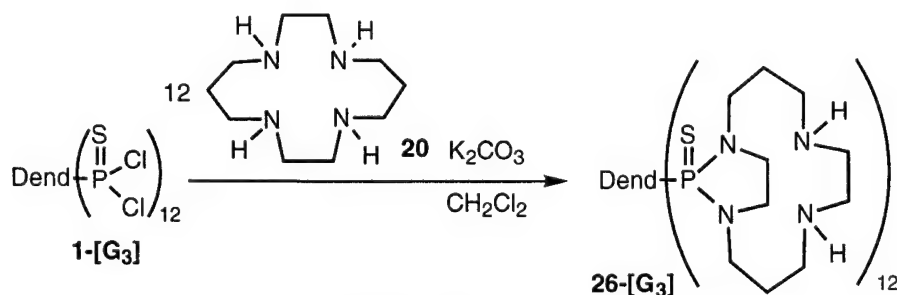
**Scheme 18**



**Figure 2**: Structure of macrocycle **2 5** determined by X-ray diffraction studies

Such experiments were extrapolated to the reaction of the dendrimer of generation 1, **1-[G$_1$]** with macrocycles **20**, **22** and **24** (Scheme 19). The expected tris macrocyclic species **26-[G$_1$]**, **28-[G$_1$]** (or **28'-[G$_1$]**), and **29-[G$_1$]** were obtained in 64-70% yield. Here also NMR data did not allowed us to choose between the two possible forms **28-[G$_1$]** or **28'-[G$_1$]**.



**Scheme 19**

We have already demonstrated that the reactivity of functional groups grafted on the surface of dendrimers of high generations is similar to those of the same functional groups anchored at the periphery of the dendrimer of generation 1. Therefore, the anchorage of 12 units of macrocycle **20** on the surface of the dendrimer of generation 3, **1-[G$_3$]** (12 terminal P(S)Cl$_2$ groups) was attempted, and allowed to isolate dendrimer **26-[G$_3$]**. Remarkably, no cross linking reactions are detected (Scheme 20).



**Scheme 20**

# C - Conclusion

We have succeeded in grafting various functional groups on the surface of phosphorus containing dendrimers, up to the fifth generation in most cases (up to 96 terminal functional groups). The nature of the terminal groups strongly influence the solubility of dendrimers. Thus, the first generation with 6 $CH(OH)P(O)[O(CH_2)_{11}CH_3]_2$ end groups is soluble in pentane (the fifth is not), whereas dendrimers with $CH(OH)P(O)(OEt)_2$ end groups are soluble in methanol, and dendrimers with $CH=CH-C(O)OLi$ end groups (not isolated) are soluble in water. Other common solvents usable, depending on the nature of the end groups, are toluene, benzene, ether, dichloromethane, chloroform, tetrahydrofurane, dioxane, or acetonitrile.

All the dendrimers isolated possess terminal end groups which confer to these macromolecules the expected properties mainly in the field of adhesives, flame retardants, additives, or sequestring agents. Furthermore, it is clear that the procedures experimented for this work should be extended to other types of functional groups to be grafted on the surface, but also in the internal caviries of some of the internaly functionalized dendrimers we now develop in the group.

It should be also emphasized that, as we have received the authorization to publish from the US Army Office, most of this work will appear in two papers: the work concerning all phosphorus end groups (excluding vinylphosphonates) is in press in the *Journal of Organic Chemistry*[3a], and the work concerning the Wadsworth-Horner-Emmons reaction, which has been extended to other functional groups, is accepted as a feature article in *Synthesis*[3b].

# D - Literature Cited

[1] – for reviews on dendrimers, see for example:

(a) Tomalia, D. A.; Naylor, A. M.; Goddart III, W. A. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 138.

(b) Tomalia, D. A.; Durst, H.D. in *Topics in Current Chemistry*, vol. 165; *Supramolecular Chemistry 1: Directed Synthesis and Molecular Recognition*; Weber, E., Ed.; Springer Verlag: Berlin, Heidelberg, **1993**, 193-313.

(c) Issberner, J.; Moors, R.; Vögtle, F. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2413.

(d) Moorefield, C. N.; Newkome, G. R. in *Advances in Dendritic Molecules*, Newkome, G. R., Ed.; JAI Press, Greenwich CT, USA **1994**, vol. 1, p 1.

(e) Ardoin, N.; Astruc, D. *Bull. Soc. Chim. Fr.* **1995**, *132*, 876.

(f) Fréchet, J.M.J.; Hawker, C.J. in: *Comprehensive Polymer Science*, 2nd suppl. **1996**, chapter 3, 71.

(g) Newkome, G.R.; Moorefield, C.N.; Vögtle, F. in: *Dendritic molecules*, VCH Weinheim **1996**.


[2] - (a) Launay, N.; Caminade, A.M.; Lahana, R.; Majoral, J.P. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1589.

(b) Launay, N.; Caminade, A.M.; Majoral, J.P. *J. Am. Chem. Soc.* **1995**, *117*, 3282.

(c) Galliot, C.; Prévoté, D.; Caminade, A.M.; Majoral, J.P. *J. Am. Chem. Soc.* **1995**, *117*, 5470.

(d) Slany, M.; Bardají, M.; Casanove, M.J.; Caminade, A.M.; Majoral, J.P.; Chaudret, B. *J. Am. Chem. Soc.* **1995**, *117*, 9764.

(e) Caminade, A.M.; Majoral, J.P. *Main Group Chemistry News* **1995**, *3*, 14.

(f) Launay, N.; Galliot, C.; Caminade, A.M.; Majoral, J.P. *Bull. Soc. Chim. Fr.* **1995**, *132*, 1149.

(g) Kraemer, R.; Galliot, C.; Mitjaville, J.; Caminade, A.M.; Majoral, J.P. *Heteroatom. Chem.* **1996**, *7*, 149.

(h) Caminade, A.M.; Slany, M.; Launay, N.; Lartigue, M.L.; Majoral, J.P. *Phosphorus, Sulfur and Silicon* **1996**, *109-110*, 517.

(i) Launay, N.; Slany, M.; Caminade, A.M.; Majoral, J.P. *J. Org. Chem.* **1996**, *61*, 3799.

(j) Majoral, J.P.; Caminade, A.M. *Actu. Chim.* **1996**, 13.

(k) Lartigue, M.L.; Slany, M.; Caminade, A.M.; Majoral, J.P. *Chemistry Eur. J.* **1996**, *2*, 1417.

(l) Slany, M.; Caminade, A.M.; Majoral, J.P. *Tetrahedron Lett.* **1996**, *37*, 9053.

(m) Bardají, M.; Kustos, M.; Caminade, A.M.; Majoral, J.P.; Chaudret B. *Organometallics* **1997**, *16*, 403.

(n) Larré, C.; Caminade, A.M.; Majoral, J.P. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 596.

(o) Slany, M.; Bardaji, M.; Caminade, A.M.; Chaudret, B.; Majoral, J.P. *Inorg. Chem.* **1997**, *36*, 1939.

(p) Launay, N.; Caminade, A.M.; Majoral, J.P. *J. Organomet. Chem.* **1997**, *529*, 51.

## [3] - **Publications issued from this report**

(a) Phosphate, phosphite, ylide and phosphonate terminated dendrimers

Prévôté, D.; Caminade, A.M.; Majoral, J.P. *J. Org. Chem.* (in press).

(b) Application of the Horner-Wadsworth-Emmons reaction to the functionalization of dendrimers: Synthesis of amino acid terminated dendrimers

Prévôté, D.; Le Roy-Gourvenec, S.; Caminade, A.M.; Masson, S.; Majoral, J.P. *Synthesis* (accepted).

# Appendixes

## List of Participating Scientific Personnel

- Dr. Jean-Pierre Majoral (20 %)

- Dr. Anne-Marie Caminade (20 %)

- Miss Delphine Prévoté (80 %)

# Phosphate-, Phosphite-, Ylide-, and Phosphonate-Terminated Dendrimers

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*Received January 30, 1997*

Many types of tri- and tetracoordinated phosphorus derivatives have been grafted on the surface of dendrimers, starting from aldehyde terminal functions. Depending on the solubility of the resulting phosphorylated dendrimers, these experiments have been carried out on generation 1 (six end groups) for phosphate- (4-[G₁]), phosphinite- (6-[G₁]), and ylide-terminated (11-[G₁]) dendrimers and up to generation 5 (96 end groups) for aminophosphate- (8-[G₁], 8-[G₅]), aminophosphite (10-[G₁], 10-[G₅]), and functionalized phosphonate-terminated (14-[G₁]–14-[G₅], 15-[G₁], 15-[G₅], 17-[G₁], 19-[G₁], 19-[G₅]) dendrimers. Most of the phosphonate-terminated dendrimers present an unexpected long-range phosphorus−phosphorus coupling constant through seven bonds ($3.8 < {}^7J_{PP} < 4.5$ Hz).

## Introduction

Tetracoordinated organophosphorus derivatives such as phosphates and phosphonates offer a wide range of applications as pesticides, insecticides, herbicides, catalysts, lubricants, adhesives, flame retardants, etc. For many uses, these compounds are grafted on polymers or are polymerized themselves. Owing to their potential applications, we decided to graft several types of tetracoordinated organophosphorus derivatives on a new class of monodisperse and highly branched polymers, namely dendrimers.[1] Our efforts were first directed toward the grafting of phosphates and then mainly toward the grafting of phosphonates, since both types of compounds generally have similar properties, but differ in that phosphonates have a different solubility and a greater stability toward hydrolysis. We have also grafted on dendrimers several other types of organophosphorus derivatives such as aminophosphates, phosphinites, aminophosphites, and even ylides.

## Results and Discussion

The family of dendrimers we used is built from P(S)-Cl₃ as core by the repetition of two reactions, which creates OC₆H₄CH=NN(Me)P(S) linkages.[2] These compounds possess 6, 12, 24, 48, or 96 terminal functions for generations 1, 2, 3, 4, or 5, respectively. These functions are either Cl or benzaldehyde groups, the latter being the starting groups for the synthesis of all the organophosphorus-terminated dendrimers described in this paper (Figure 1).

## Scheme 1



In first attempts, we tried to graft phosphate groups in two steps from the dendrimer 1-[G₁]. The first step is a condensation with hydrazine, used in very large excess, to afford compound 2-[G₁].[2d,f] The second step is another condensation, with the phosphate 3, easily obtained by reaction of hydroxybenzaldehyde sodium salt with (EtO)₂P(O)Cl (Scheme 1). The synthesis of dendrimer 4-[G₁] is monitored by ³¹P NMR, which shows a slight deshielding of the signal corresponding to the (EtO)₂P(O)R moieties on going from 3 ($\delta {}^{31}P = -7$ ppm) to 4-[G₁] ($\delta {}^{31}P = -6.7$ ppm). Additional proofs of the condensation reaction are given by ¹H NMR, with the total disappearance of signals corresponding to CHO and NH₂ groups. Furthermore, ¹³C NMR indicates the presence of two very close singlets ($\delta {}^{13}C = 160.5$ and 160.8 ppm) corresponding to the azine −CH=NN=CH− linkages of the dendrimer 4-[G₁].

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 ⊕ Abstract published in *Advance ACS Abstracts,* Xxxxxxxxx YY, ZZZZ.
 (1) For reviews on dendrimers, see, for example: (a) Tomalia, D. A.; Naylor, A. M.; Goddart, W. A., III. *Angew. Chem., Int. Ed. Engl.* **1990,** *29,* 138. (b) Tomalia, D. A. In *Topics in Current Chemistry*; Weber, E., Ed.; Springer Verlag: Berlin, Heidelberg, 1993; Vol. 165, p 193. (c) Issberner, J.; Moors, R.; Vögtle, F. *Angew. Chem.* **1994,** *106,* 2507; *Angew. Chem., Int. Ed. Engl.* **1994,** *33,* 2413. (d) Moorefield, C. N.; Newkome, G. R. In *Advances in Dendritic Molecules*; Newkome, G. R., Ed.; JAI Press: Greenwich, CT, 1994; Vol. 1, p 1. (e) Caminade, A.-M.; Majoral, J.-P. *Main Group Chem. News* **1995,** *H* 14. (f) Ardoin, N.; Astruc, D. *Bull. Soc. Chim. Fr.* **1995,** *132,* 876. (g) Majoral, J.-P.; Caminade, A.-M. *Acta Chim.* **1996,** *4,* 13. (h) Fréchet, J. M. J.; Hawker, C. J. In *Comprehensive Polymer Science*: 1996; 2nd Suppl., Chapter 3, p 71.

(2) (a) Launay, N.; Caminade, A. M.; Lahana, R.; Majoral, J. P. *Angew. Chem., Int. Ed. Engl.* **1994,** *33,* 1589. (b) Launay, N.; Caminade, A. M.; Majoral, J. P. *J. Am. Chem. Soc.* **1995,** *117,* 3282. (c) Slany, M.; Bardaji, M.; Casanove, M. J.; Caminade, A. M.; Majoral, J. P.; Chaudret, B. *J. Am. Chem. Soc.* **1995,** *117,* 9764. (d) Launay, N.; Slany, M.; Caminade, A. M.; Majoral, J. P. *J. Org. Chem.* **1996,** *61,* 3799. (e) Lartigue, M. L.; Slany, M.; Caminade, A. M. Majoral, J. P. *Chem. Eur. J.* **1996,** *2,* 1417. (f) Bardaji, M.; Kustos, M.; Caminade, A. M.; Majoral, J. P.; Chaudret, B. *Organometallics* **1997,** *16,* 403. (g) Slany, M.; Caminade, A. M.; Majoral, J. P. *Tetrahedron Lett.* **1996,** *37,* 9053.
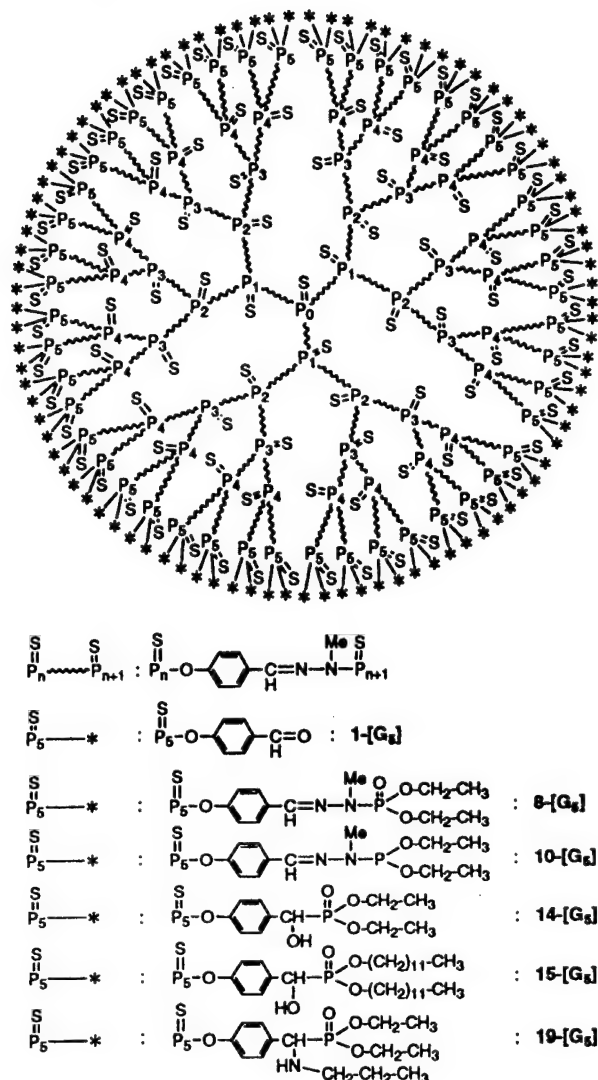
**Figure 1.** Fifth generation of the dendrimer with various end groups.

We tried to extend this reaction to higher generations 4-[$G_n$] (*n*: generations 2–5). Unfortunately, the condensation results in all cases in the formation of powders, insoluble in water and in common organic solvents. However, the same condensation reaction can be applied to graft other phosphorus derivatives such as phosphinites. Indeed, the phosphinite **5**, obtained by reaction of hydroxybenzaldehyde and triethylamine and diphenylchlorophosphine, is easily condensed with dendrimer 2-[$G_1$] to afford the phosphinite-terminated dendrimer 6-[$G_1$] (Scheme 2). The condensation induces a slight shielding of the signal corresponding to the Ph$_2$PO moieties in $^{31}$P NMR on going from **5** ($\delta^{31}$P = 112.3 ppm) to 6-[$G_1$] ($\delta^{31}$P = 111.5 ppm) and the total disappearance of signals corresponding to CHO and NH$_2$ groups in $^1$H NMR. In this case also, we tried to obtain higher generations of the phosphinite-terminated dendrimers, for instance 6-[$G_3$], but we observed the same phenomenon of insolubility that we already noted for dendrimers 4-[$G_n$] (*n* > 1), probably due to the presence of many diarylazine groups. To overcome this problem, we decided to avoid the formation of this linkage and, therefore,

**Scheme 2**



**Scheme 3**



from y = 6 for [$G_1$] to y = 96 for [$G_5$]
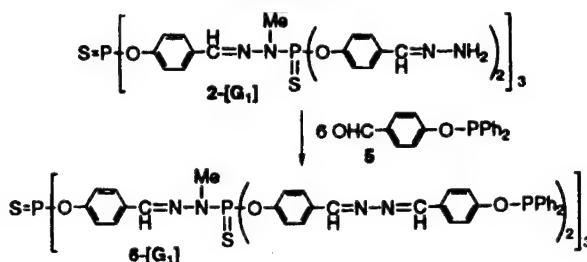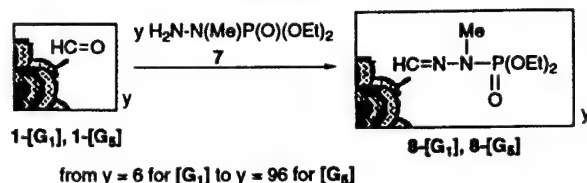
**Scheme 4**
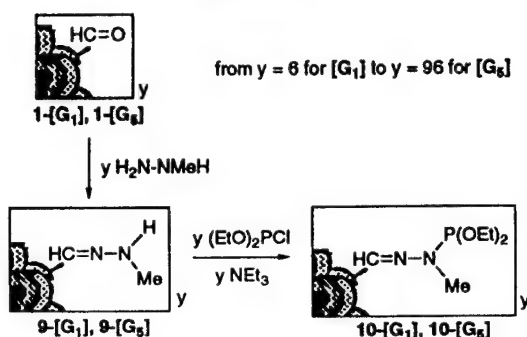


to find other strategies to graft phosphorus derivatives on the dendrimer.

We tried first another condensation reaction, with aldehyde groups on the dendrimer and NH$_2$ groups on the phosphorus derivative to be grafted, such as H$_2$NN-(Me)P(O)(OEt)$_2$ **7**. This compound, obtained by reaction of methylhydrazine with ClP(O)(OEt)$_2$, reacts easily with the first generation of the dendrimer 1-[$G_1$] (6 CHO end groups) but also with the fifth generation 1-[$G_5$] (96 CHO end groups) (Scheme 3, Figure 1). In both cases, the quantitative formation of the hydrazonophosphate-terminated dendrimer 8-[$G_n$] is monitored by $^{31}$P NMR. Indeed, we observed the total disappearance of the signal corresponding to **7** ($\delta^{31}$P = 8.7 ppm) on behalf of the appearance of a new signal ($\delta^{31}$P = 2.8 ppm) corresponding to the P=O groups of 8-[$G_n$]. Furthermore, the signal of the phosphorus atoms on the external layer of the dendrimer (P$_1$ for [$G_1$], P$_5$ for [$G_5$]) is slightly deshielded on going from 1-[$G_n$] to 8-[$G_n$] ($\Delta\delta$ = 2.2 ppm). The total disappearance of signals corresponding to CHO and NH$_2$ groups in $^1$H NMR confirms the quantitative formation of dendrimers 8-[$G_n$] as crude product. It is worth noting that the fifth generation of the dendrimer 8-[$G_5$], which possesses 96 hydrazonophosphate groups, remains perfectly soluble in several organic solvents such as THF, chloroform, dichloromethane, etc.

Obviously, many types of phosphorus derivatives can be grafted on the surface of the dendrimers in this way, provided the formation of the phosphorohydrazide H$_2$-NNMeP(X)R$_2$ could be accomplished. This is the case with most P$^{IV}$ derivatives (X = O, S, N...) but is extremely difficult and even impossible with P$^{III}$ derivatives. In-

**Scheme 5**



**9-[G₁]** (appears as **9-[G$_1$]**)

**12-[G$_1$]**

**11-[G$_1$]**

**13-[G$_1$] (90% *trans-trans*)**
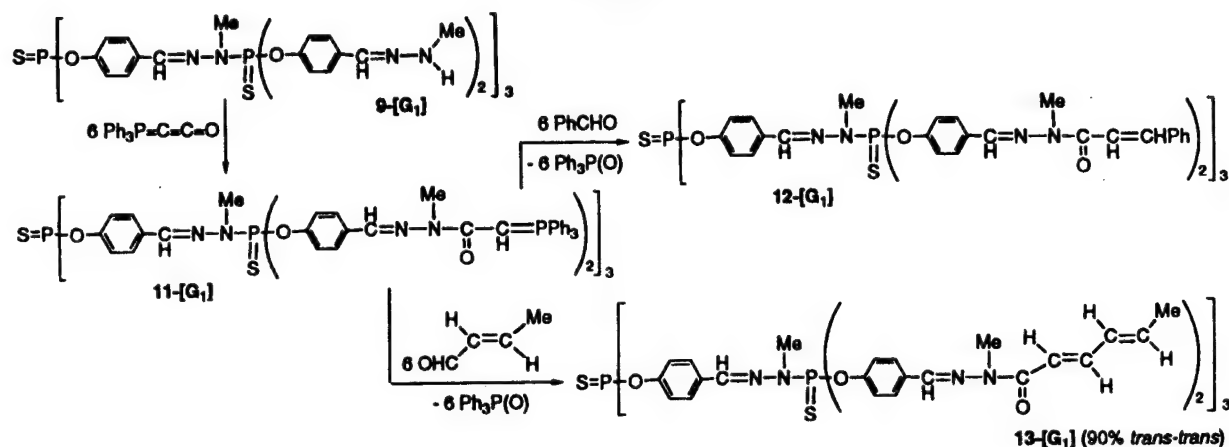
deed, the higher reactivity of tricoordinated phosphorus precludes the specificity of the reaction on the NHMe group of methylhydrazine, which is observed with tetra-coordinated phosphorus. However, another strategy can be applied, for instance, to graft hydrazinophosphites, in two steps. The first step is the condensation of 1-[G$_n$] with methylhydrazine, which affords dendrimers 9-[G$_n$].[2b-d] The second step consists of grafting (EtO)$_2$-PCl in the presence of NEt$_3$, which yields the hydrazono-phosphite-terminated dendrimers 10-[G$_n$] (Scheme 4, Figure 1). These reactions have been applied to generation 1 (10-[G$_1$]: 6 N–P(OEt)$_2$ end groups) and generation 5 (10-[G$_5$]: 96 N–P(OEt)$_2$ end groups) in the same conditions. Both compounds are particularly characterized by the appearance of a new singlet in $^{31}$P NMR ($\delta^{31}$P = 139 ppm, NP(OEt)$_2$) and by the shielding of the terminal NMe groups in $^{13}$C NMR on going from 9-[G$_n$] ($\delta^{13}$d = 34.0 ppm, –NMeH) to 10-[G$_n$] ($\delta^{13}$C = 28.4 ppm, –NMeP$^{III}$).

All the experiments described above allow to bind phosphorus groups to the dendrimer by means of O or N linkages; we have thus isolated dendrimers with phosphate (OP(O)[OR]$_2$), phosphinite (OPR$_2$), aminophosphate (NP(O)[OR]$_2$), or aminophosphite (NP[OR]$_2$) end groups. In previous papers, we already described the use of carbon–phosphorus bonds to graft phosphines (CH$_2$-PR$_2$).[2c,f,g] It appeared interesting to extend this work to the grafting of other types of phosphorus derivatives with C–P bonds, particularly ylides and phosphonates because of their numerous applications in different fields.

Dendrimers 9-[G$_n$] may be used as the starting material for the grafting of ylides. Indeed, it is known that triphenylphosphoranylidene ethenone Ph$_3$P=C=C=O undergoes the addition of compounds with acidic hydrogens, such as alcohols, thiols, or amines, to the C=C bond.[3] Application of this type of addition to dendrimer 9-[G$_1$] affords the ylide-terminated dendrimer 11-[G$_1$] (Scheme 5). This compound is characterized in particular by the presence of the signal of the ylide moieties in $^{31}$P NMR ($\delta^{31}$P = 18.3 ppm), whereas $^{13}$C NMR displays the presence of amido groups ($\delta^{13}$C = 170.3 ppm, d, $^2J_{CP}$ = 26.8 Hz) and a slight deshielding of the signal corresponding to the NMe end groups ($\delta^{13}$C = 26.8 ppm). In view of the widespread use of ylides in organic chemistry, it would have been interesting to synthesize higher generations of dendrimers with ylide end groups; thus,

we tried to obtain the same type of compound from the second generation 9-[G$_2$]. Unfortunately, the corresponding ylide-terminated dendrimer 11-[G$_2$] was found to be insoluble in water and in a variety of organic solvents, in.

However, we decided to test the reactivity of the first generation 11-[G$_1$] in the Wittig reaction, toward benzaldehyde and crotonaldehyde. Benzaldehyde reacts at room temperature to afford compound 12-[G$_1$] in quantitative yield as crude product (Scheme 5). The reaction is monitored by $^{31}$P NMR, which indicates the total disappearance of the ylide signal on behalf of the appearance of the signal corresponding to Ph$_3$P(O) ($\delta^{31}$P = 24 ppm). After removal of the triphenylphosphine oxide, $^1$H NMR indicates a slight deshielding of the signal corresponding to the CH$_3$NCO groups, but the signals of the CH=CH linkages are overlapped by the aromatic signals and did not allow us to determine the geometry of the ethylenic linkage. However, $^{13}$C NMR indicates the formation of both cis and trans isomers; indeed, each carbon atom of the CH$_3$NC(O)CH=CH– linkages gives two close singlets, approximately in a 1:3 ratio, whereas for all the other parts of the dendrimer 12-[G$_1$], each carbon gives a single set of signals. According to the known tendency of stabilized ylides to give predominantly trans isomers in the Wittig reaction,[4] we tentatively assign the largest signals to the trans isomer.

This assignment is corroborated by the study of the reaction of crotonaldehyde (trans isomer) with 12-[G$_1$] (Scheme 5). In this case also, $^{13}$C NMR displays the formation of two isomers, characterized by the presence of two signals for each carbon atom of the CH$_3$NC(O)-CH=CHCH=CHMe linkages in an approximate 1:9 ratio. The attribution of these signals to the cis-trans and trans-trans isomers, respectively, is unambiguous in this case owing to $^1$H two-dimensional NMR experiments. Indeed, two doublets in a 1:9 ratio are observed for the H$_d$ protons of the CH$_d$=CH$_c$CH$_b$=CH$_a$Me linkages: $\delta$ $^1$H = 6.80 (d, $^3J_{HdHc}$ = 10.0 Hz), and 7.12 (d, $^3J_{HdHc}$ = 15.0 Hz) ppm. The value of the coupling constants allows us to attribute unambiguously the former signals to the minor cis-trans isomer and the latter to the major trans-trans isomer.

The last type of phosphorus derivatives we tried to graft on dendrimers is phosphonates. In all cases, the

(3) Bestmann, H. J. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 349.

(4) Johnson, A. W.; Kaska, W. C.; Starzewski, K. A. O.; Dixon, D. A. In *Ylides and imines of phosphorus*; Johnson, A. W., Ed.; John Wiley & Sons, Inc.: New York, 1993; Chapter 8.
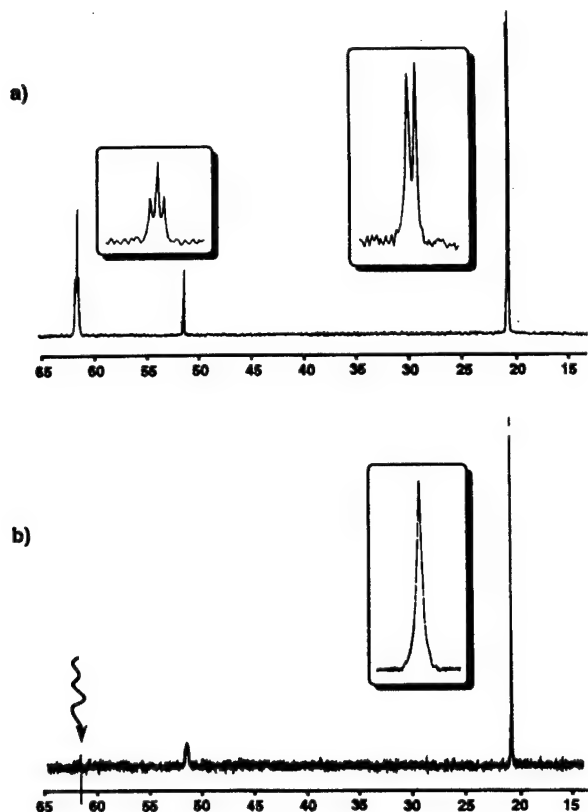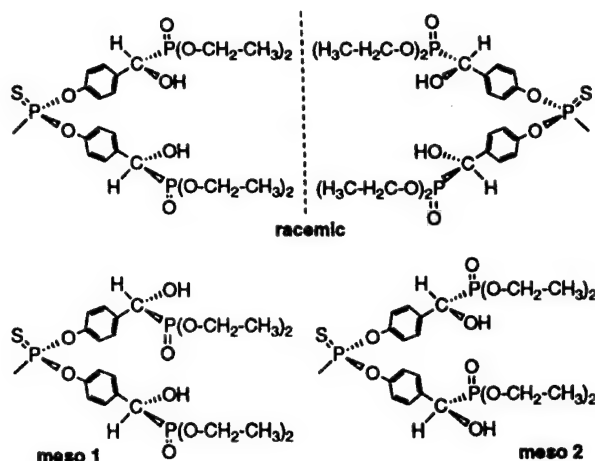
**Figure 2.** (a) $^{31}$P{$^1$H}NMR spectra of dendrimer **14-[G$_1$]**. (b) $^{31}$P{$^1$H}NMR spectra of dendrimer **14-[G$_1$]** with selective irradiation of the signal at $\delta = 62$ ppm.

method of synthesis we used consists of the addition of P–H bonds on polar double bonds of the dendrimer. In our first attempts, we tried to graft phosphonate groups by addition of diethyl phosphite to the aldehyde functions of dendrimer **1-[G$_1$]** in several conditions, using THF as solvent. It is well known that this type of reaction is catalyzed by bases;[5] thus, we used either CsF, NEt$_3$, or DBU as catalysts, heating for several days at 65 °C. In all cases, we observed only a partial reaction, even after heating for 2 weeks (when CsF is used), or a degradation (when DBU is used). On the other hand, when a large excess of diethyl phosphite is used without solvent, and in the presence of CsF as catalyst under heating, the reaction with **1-[G$_1$]** goes to completion. However, the resulting α-hydroxy methylphosphonate-terminated dendrimer **14-[G$_1$]** is difficult to purify in these conditions, both from CsF and from the large excess of diethyl phosphite.

We also tried to use NEt$_3$ as catalyst (20–40%) without solvent, the dendrimer **1-[G$_1$]** being dissolved in the mixture Et$_3$N/(EtO)$_2$P(O)H. In these conditions, the reaction proceeds rapidly and quantitatively at room temperature, and the resulting phosphonate-terminated dendrimer **14-[G$_1$]** is more easily purified (Scheme 6). However, the $^{31}$P NMR spectrum of compound **14-[G$_1$]** appears surprisingly complex. Indeed, beside the singlet corresponding to the phosphorus of the core ($\delta$ $^{31}$P = 51.8 ppm, P$_0$), we observed two signals centered at $\delta = 21.3$ ppm, corresponding to P(O)(OEt)$_2$, and three signals centered at $\delta = 62.0$ ppm, corresponding to the phospho-

(5) See, for instance, Abramov, V. S. *Zh. Obsch. Khim.* **1957**, *27*, 169; (*Chem. Abstr.* **1957**, *51*, 12878e).



**Figure 3.** Racemic and meso forms for each branch of dendrimers **14-[G$_n$]**.

**Scheme 6**
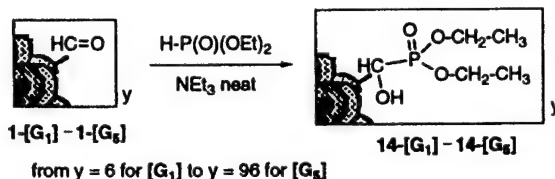


rus of the first generation P$_1$ (Figure 2a). At first glance, these signals could be due to the formation of three diastereoisomers (one racemic and two meso forms) for each branch of the dendrimer, as the addition of PH groups to aldehydes creates chiral carbon centers (Figure 3). However, the relative intensity for each set of signals (1:2:1 for $\delta = 62.0$ ppm and 1:1 for $\delta = 21.3$ ppm) and the line separation seems to be in agreement with the presence of a triplet and a doublet, with a coupling constant of 3.9 Hz, which should correspond to the coupling of P$_1$(S) with P(O) through seven bonds! This surprising result prompted us to verify this hypothesis by selective phosphorus-decoupling NMR experiments. The selective irradiation of the signal at $\delta = 62.0$ ppm clearly induces the transformation of the signal at $\delta = 21.3$ ppm from a doublet to a singlet (Figure 2b). Furthermore, the selective irradiation of the signal at $\delta = 21.3$ ppm also transforms the signal at $\delta = 62.0$ ppm to a singlet. These experiments confirm the existence of the $^7J_{PP}$ coupling constant in compound **14-[G$_1$]**. Very few coupling constants through so many bonds have been reported in the literature, most of them concerning through-space couplings,[6] which are unlikely for compound **14-[G$_1$]** for steric reasons. However, a phosphorus–phosphorus coupling constant over seven bonds has already been measured for a compound whose structure is closely related to that of **14-[G$_1$]**: the analysis of the outer $^{13}$C satellites in the $^{31}$P NMR spectrum of (EtO)$_2$P(O)CH$_2$C$_6$H$_4$CH$_2$P(O)(OEt)$_2$ gave $^7J_{PP} = 7.8$ Hz, a value attributed to a large Π-electron contribution.[7] The value directly obtained in the case of **14-[G$_1$]** ($^7J_{PP} = 3.9$ Hz) compares well with these data.
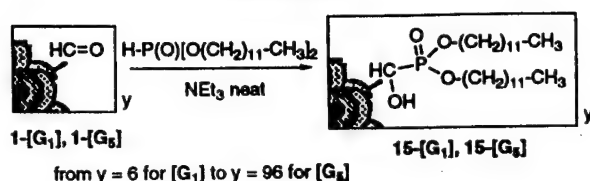
(6) (a) Szalontai, G.; Bakos, J.; Toth, I.; Heil, B. *Magn. Reson. Chem.* **1987**, *25*, 761. (b) Pastor, S. D.; Hyun, J. L.; Odorisio, P. A.; Rodebaugh, R. K. *J. Am. Chem. Soc.* **1988**, *110*, 6547. (c) Pastor, S. D.; Shum, S. P.; DeBellis, A. D.; Burke, L. P.; Rodebaugh, R. K.; Clarke, F. H.; Rihs, G. *Inorg. Chem.* **1996**, *35*, 949 and references cited therein.
(7) Ernst, L. *J. Chem. Soc., Chem. Commun.* **1977**, 375. (b) Ernst, L. *Org. Magn. Reson.* **1977**, *1*, 35.

**Scheme 7**



1-[G₁], 1-[G₅]                           15-[G₁], 15-[G₅]

from y = 6 for [G₁] to y = 96 for [G₅]

**Scheme 8**



**Scheme 9**



The grafting of phosphonate groups can be extended to higher generations without any problem of solubility. We have carried out this reaction under the same conditions for all the generations from 1 to 5 and, thus, isolated dendrimers $14\text{-}[G_1]\text{-}14\text{-}[G_5]$, with up to 96 phosphonate end groups (Scheme 6). In all cases, we observed a doublet in the $^{31}P$ NMR spectra at $\delta = 21$ ppm ($3.8 < {}^7J_{PP} < 4.5$ Hz) for the P(O)(OEt)₂ groups, whereas the signal at $\delta = 62$ ppm becomes a broad singlet for generations higher than 2, presumably due to the formation of an increasing number of stereoisomers. The full transformation of the aldehyde groups in alcohol for all compounds is characterized in $^1H$ NMR by the total disappearance of the singlet of the aldehyde groups on behalf of the appearance of a doublet at *ca.* 5 ppm corresponding to the C*HOH groups. The presence of chiral carbon atoms also complicates the $^1H$ and $^{13}C$ NMR spectra for all generations, as this renders the CH₂CH₃ groups diastereotopic. This is clearly seen in $^{13}C$ NMR spectra by the presence of two distinct doublets at *ca* 63–65 ppm corresponding to the OCH₂CH₃ groups.

The facility of the synthesis of dendrimers $14\text{-}[G_1]\text{-}14\text{-}[G_5]$ incited us to try to extend this reaction to other phosphonates and to other end groups on the dendrimers. For instance, the long chain phosphonate HP(O)[O(CH₂)₁₁-CH₃]₂ also reacts with dendrimers 1-[G₁] and 1-[G₅] to afford dendrimers 15-[G₁] and 15-[G₅] (Scheme 7). These compounds possess the same spectral characteristics already noted for dendrimers $14\text{-}[G_1]\text{-}14\text{-}[G_5]$, in particular, a ${}^7J_{PP} = 3.8$ Hz is clearly observed on the $^{31}P$ NMR spectrum of 15-[G₁]. The presence of several long-chain hydrocarbons modifies the solubility of the dendrimer: for instance, compound 15-[G₁] is soluble in pentane, whereas none of the dendrimers we already synthesized is.

We also tried the addition of phosphonates on a dendrimer with α,β-unsaturated aldehydes as end groups, 16-[G₁]. This compound is obtained in THF at 40 °C by reacting 6 equiv of the sodium salt of 4-hydroxy-3-methoxycinnamaldehyde with (S)P[OC₆H₄CH=NN(Me)P-(S)Cl₂]₃ (Scheme 8). Addition of HP(O)(OEt)₂ on 16-[G₁] affords dendrimer 17-[G₁], which possesses six unsaturated alcohol–phosphonate end groups. In this case, no phosphorus–phosphorus coupling constant through nine bonds is observed on the $^{31}P$ NMR spectrum of 17-[G₁]. $^1H$ NMR shows the total disappearance of the CHO groups on behalf of the appearance of a doublet of doublet at $\delta = 4.6$ ppm ($^2J_{HP} = 13.4$ Hz, $^3J_{HH} = 5.0$ Hz) corresponding to C*HOH. As expected, no reaction occurred on the CH=CH bonds.

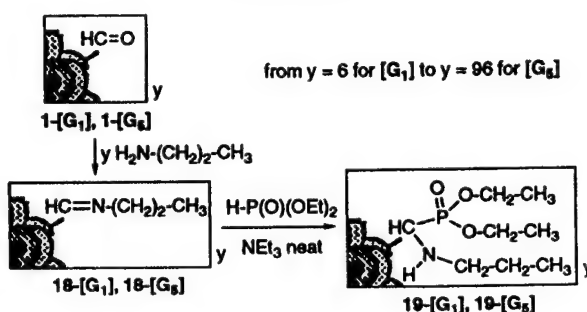IR spectra of compounds $14\text{-}[G_1]\text{-}14\text{-}[G_5]$, 15-[G₁], 15-[G₅], and 17-[G₁] exhibit classical $\nu_{OH} \simeq 3270$ cm⁻¹, demonstrating the presence of a hydrogen bond between hydroxyl and phosphoryl groups.

Finally, we also tried to add phosphonates to imine terminal functions, as it is known that this type of reaction proceeds approximately under the same condi-

tions as the addition to aldehydes.[8] For this purpose, we synthesized first the imine-terminated dendrimers 18-[G₁] and 18-[G₅], easily obtained by condensation of propylamine with dendrimers 1-[G₁] and 1-[G₅], respectively (Scheme 9). Addition of HP(O)(OEt)₂ on dendrimers 18-[G₁] and 18-[G₅] at room temperature affords dendrimers 19-[G₁] and 19-[G₅], respectively. In this case also, the phosphorus–phosphorus coupling constant through seven bonds (${}^7J_{PP} = 4.5$ Hz) is clearly observed on the $^{31}P$ NMR spectra of both generations. The reaction has gone to completion, as demonstrated by the total disappearance of the imine functions ($\delta = 8.20$ ppm) in $^1H$ NMR. The addition to the imine bonds is chemoselective; no reaction occurs on the hydrazone functions of the skeleton of the dendrimer, either in this experiment or in all the previous cases.
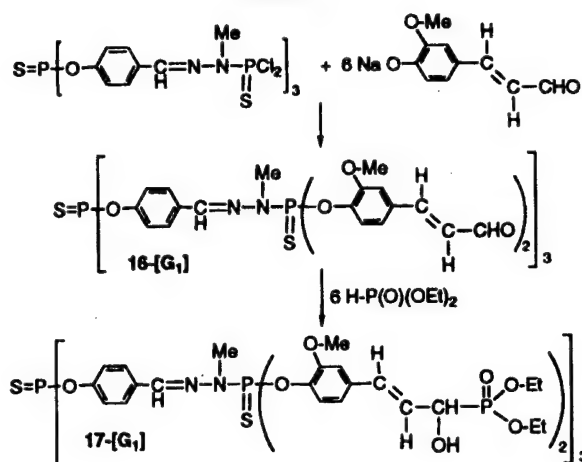
**Conclusion**

We have experimented with several strategies to graft tri- and tetracoordinated phosphorus derivatives on dendrimers of generation one–five, depending on the solubility of the resulting dendrimer. It can be inferred from all these experiments that the solubility of the dendrimers depends essentially on the type of substituents grafted on the surface. Indeed, azinephosphate, azinephosphinite, and ylide linkages on the periphery dramatically reduce the solubility of dendrimers possessing more than six end groups. On the other hand, the grafting of long-chain hydrocarbons increases the solubility of the dendrimer in organic solvents. However, it can

(8) See, for instance: (a) Fields, E. K. *J. Am. Chem. Soc.* **1952**, *74*, 1528. (b) Caccamese, S.; Failla, S.; Finocchiaro, P.; Hägele, G.; Principato, G. *J. Chem. Res., Synop.* **1992**, 242.

be pointed out that each end group seems to behave independently as far as the reactivity is concerned. Moreover, the reactivity of the ylide-terminated dendrimer with aldehydes follows the rules elaborated for classical Wittig reactions in organic chemistry.

The phosphonate-terminated dendrimers appears to be very interesting, as all of them remain soluble in common organic solvents, even for high generations. Furthermore, the addition reaction we used allows several variations, both in the nature of the phosphonate to be grafted and in the nature of the polar double bond on the surface of the dendrimer. It is also worth noting that this reaction creates additional functions on the surface on the dendrimer, besides the phosphonate groups: alcohols or secondary amines groups, whose reactivity should be interesting to investigate. Furthermore, these compounds possess a rare and unexpected long-range phosphorus–phosphorus coupling constant through seven bonds for the $(S)POC_6H_4CHRP(O)(OR')_2$ linkages (R = OH, NHPr; R' = Et, $(CH_2)_{11}CH_3$).

To summarize, this work clearly demonstrates for the first time that it is possible to anchor to the surface of dendritic molecules a large variety of phosphorus groups (phosphates, phosphites, hydrazonophosphates, hydrazonophosphites, phosphorus ylides, and phosphonates (from 6 to 96 units), each of them having potentially a great interest in different fields. Indeed, biologically important phosphates are known (nucleotides, phospholipides, nucleosides, polyphosphates, phosphate sugars);[9,10] phosphite monomers are used in some catalytic processes (acrylonitrile dimerization) and in the well-known Arbusov rearrangement,[11] while phosphorus ylides play a key role in Wittig reactions.[11] Moreover, phosphonate monomers have found wide applications in general organic synthesis[12-14] (Horner–Wadsworth–Emmons condensation, Diels–Alder reactions, Michael additions, etc.), and they can be used as versatile intermediates for the preparation of a number of heterocycles.[14]

Work is in progress to study the properties of these new terminated dendrimers in some of the areas reported above and to extend the scope of reactions developed in this paper to other types of phosphorus derivatives.

## Experimental Section

**General Methods.** All manipulations were carried out with standard high vacuum or dry argon atmosphere techniques. $^1H$, $^{31}P\{^1H\}$, and $^{13}C\{^1H\}$ NMR spectra were recorded on Bruker AC 200 or WM 250 or AMX 400 spectrometers, using CDCl$_3$ as solvent, except where noted. $^{31}P$ NMR chemical shifts are reported in ppm relative to 85% H$_3$PO$_4$. Coupling constants ($J$) are reported in $H_z$.

**Synthesis of Compound 3.** To a solution of 4-hydroxybenzaldehyde sodium salt (0.500 g, 3.47 mmol) in THF (10 mL) was added (EtO)$_2$P(O)Cl (0.500 mL, 3.47 mmol). The resulting mixture was stirred for 1 h at room temperature and then filtered to give an oil that was used without further purification.

**3:** colorless oil; 70% yield (0.627 g); $^{31}P$ NMR $\delta$ −7.0; $^1H$ NMR $\delta$ 1.04 (t, $J$ = 7.0, 6H), 3.92 (q, $J$ = 7.0, 2H), 3.96 (q, $J$ = 7.0, 2H), 7.08 (dd, $J$ = 8.5, 2H), 7.58 (dd, $J$ = 8.5, 2H), 9.65 (s,

(9) Engel, R. *Chem. Rev.* **1977**, *77*, 349.
(10) Klachburn, G. M.; Peree, T. D.; Rashid, A.; Bisbal, C.; Lebleu, B. *Chem. Scripta* **1986**, *26*, 21.
(11) *Methoden der Organischen Chemie (Houben-weyl E1)*; Regitz, M., Ed.; Georg Thieme Verlag: Stuttgart, 1982.
(12) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73.
(13) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.
(14) Minami, T.; Motoyoshiya, J. *Synthesis* **1992**, 333.

1H); $^{13}C$ NMR $\delta$ 15.6 (d, $J$ = 6), 64.6 (d, $J$ = 6), 120.2 (d, $J$ = 5), 131.3, 132.9, 155.0 (d, $J$ = 7), 190.4.

**Synthesis of Phosphate-Terminated Dendrimer 4-[G$_1$].** To a solution of 0.200 g of dendrimer **2-[G$_1$]** (0.133 mmol) in THF (10 mL) was added phosphate **3** (0.206 g, 0.798 mmol). The resulting mixture was stirred overnight at room temperature and then evaporated to dryness to give a yellow powder. This powder was washed with pentane/ether (1/1).

**4-[G$_1$]:** yellow powder; 72% yield (0.282 g); $^{31}P$ NMR $\delta$ −6.7, 52.0, 61.2; $^1H$ NMR $\delta$ 1.33 (m, 36H), 3.36 (d, $J$ = 9.8, 9H), 4.19 (m, 24H), 7.26−7.78 (m, 63H), 8.56 (br s, 12H); $^{13}C$ NMR $\delta$ 15.9 (d, $J$ = 6), 32.8 (d, $J$ = 16), 64.6 (d, $J$ = 6), 120.2 (d, $J$ = 5), 121.3, 121.7 (d, $J$ = 4), 128.3, 129.8, 129.9, 130.6, 131.2, 138.4 (d, $J$ = 14), 150.5 (d, $J$ = 9), 152.5 (d, $J$ = 9), 152.7 (d, $J$ = 9), 160.5, 160.8. Anal. Calcd for C$_{132}$H$_{144}$N$_{18}$O$_{33}$P$_{10}$S$_4$: C, 53.77; H, 4.92; N, 8.55. Found: C, 53.63; H, 4.89; N, 8.47.

**Synthesis of Compound 5.** To a solution of 4-hydroxybenzaldehyde (0.250 g, 2.047 mmol) in THF (10 mL) were added triethylamine (0.285 mL, 2.047 mmol) and then diphenylchlorophosphine (0.367 mL, 2.047 mmol). The resulting mixture was stirred for 1 h at room temperature and then filtered and evaporated to dryness to give a pale yellow paste. This compound was used without further purification.

**5:** yellow paste; 83% yield (0.520 g); $^{31}P$ NMR $\delta$ 112.3; $^1H$ NMR $\delta$ 7.0−7.8 (m, 14H), 9.87 (s, 1H); $^{13}C$ NMR $\delta$ 118.8 (d, $J$ = 13), 128.5 (d, $J$ = 7), 130.0, 130.5 (d, $J$ = 23), 131.7, 132.1, 139.5 (d, $J$ = 17), 155.5 (d, $J$ = 9), 190.8.

**Synthesis of Phosphinite-Terminated Dendrimer 6-[G$_1$].** To a solution of dendrimer **2-[G$_1$]** (0.177 g, 0.117 mmol) in dichloromethane (10 mL) was added a solution of compound **5** (0.215 g, 0.702 mmol) in CH$_2$Cl$_2$ (4 mL) in the presence of molecular sieves (4 Å). The resulting mixture was stirred overnight at room temperature and then filtered and evaporated to dryness to give a yellow powder very sensitive to oxidation.

**6-[G$_1$]:** yellow powder; 64% yield (0.242 g); $^{31}P$ NMR $\delta$ 52.5, 61.6, 111.5; $^1H$ NMR $\delta$ 3.30 (d, $J$ = 10.5, 9H), 7.20−7.80 (m, 123H), 8.60 (br s, 12H); $^{13}C$ NMR $\delta$ 32.9 (d, $J$ = 12), 118.8 (d, $J$ = 11), 120.9, 121.6, 128.4, (d, $J$ = 7), 128.7, 129.8, 130.0 (d, $J$ = 13), 130.6, 131.5, 131.7, 138.4 (d, $J$ = 14), 140.0 (d, $J$ = 17), 151.2 (d, $J$ = 8), 152.4 (m), 161.00. Anal. Calcd for C$_{180}$H$_{144}$N$_{18}$O$_{15}$P$_{10}$S$_4$: C, 66.78; H, 4.48; N, 7.79. Found: C, 66.51; H, 4.36; N, 7.65.

**Synthesis of Compound 7.** To a solution of 0.31 mL (5.83 mmol) of methylhydrazine in THF (10 mL) was slowly added a solution of 0.42 mL (2.92 mmol) of chloro diethyl phosphite in THF (10 mL) at −90 °C. This mixture was allowed to slowly warm to room temperature. After filtration, the solvent was eliminated under vacuum to give a pale-yellow oil. This compound was used without further purification.

**7:** yellow oil; 70% yield (0.372 g); $^{31}P$ NMR $\delta$ 8.7; $^1H$ NMR $\delta$ 0.97 (t, $J$ = 7.0, 6H), 2.57 (d, $J$ = 8.8, 3H), 3.67 (q, $J$ = 7.0, 2H), 3.77 (q, $J$ = 7.0, 2H), 3.98 (br s, 2H); $^{13}C$ NMR $\delta$ 15.8 (d, $J$ = 6), 40.3 (d, $J$ = 11), 62.4 (d, $J$ = 6).

**General Procedure for the Synthesis of Aminophosphate-Terminated Dendrimers 8-[G$_1$] and 8-[G$_5$].** To a solution of 0.250 g of **1-[G$_n$]** (*n* = 1, 0.176 mmol; *n* = 5, 0.008 mmol) in THF (10 mL) was added an excess of (EtO)$_2$P(O)-NMeNH$_2$ (*n* = 1, 0.385 g, 2.11 mmol; *n* = 5, 0.280 g, 1.54 mmol) in the presence of molecular sieves (4 Å). The resulting mixture was stirred for 2 days at room temperature and then evaporated to dryness to give an oil. Addition of pentane precipitated the oil to give a white powder. Pentane was eliminated via cannula, and the powder was dried under vacuum. This powder was then washed with ether.

**8-[G$_1$]:** white powder; 65% yield (0.275 g); $^{31}P$ NMR $\delta$ 2.8, 52.7, 62.6; $^1H$ NMR $\delta$ 1.3 (br t, $J$ = 7.3, 36H), 3.2 (d, $J$ = 7.3, 18H), 3.4 (d, $J$ = 10.4, 9H), 4.0 (m, 24H), 7.1−7.8 (m, 45H); $^{13}C$ NMR $\delta$ 15.9 (d, $J$ = 7), 31.9 (d, $J$ = 10), 32.9 (d, $J$ = 13), 63.4 (d, $J$ = 6), 121.5 (d, $J$ = 5), 127.6, 128.3, 132.6, 136.7, (d, $J$ = 15), 138.3 (d, $J$ = 14), 150.7 (d, $J$ = 8), 151.0 (d, $J$ = 9). Anal. Calcd for C$_{96}$H$_{132}$N$_{18}$O$_{27}$P$_{10}$S$_4$: C, 47.88; H, 5.52; N, 10.47. Found: C, 47.79; H, 5.46,; N, 10.24.

**8-[G$_5$]:** white powder; 15% yield (0.056 g); $^{31}P$ NMR $\delta$ 2.7, 62.6 (br s); $^1H$ NMR $\delta$ 1.25 (br s, 576 H), 3.18 (d, $J$ = 6.4, 288H), 3.33 (d, $J$ = 10, 279 H), 4.05 (m, 384H), 7.14−7.65 (m, 945H);

$^{13}$C NMR $\delta$ 16.0 (d, $J = 7$), 32.0 (d, $J = 10$), 32.9 (d, $J = 14$), 63.4 (d, $J = 6$), 121.5 (d, $J = 3$), 127.6, 128.1, 132.0, 132.5, 136.8 (d, $J = 15$), 138–140 (m), 150.7 (d, $J = 7$), 151.2 (m). Anal. Calcd for $C_{1896}H_{2472}N_{378}O_{477}P_{190}S_{94}$: C, 48.36; H, 5.29; N, 11.24. Found: C, 48.17; H, 5.14; N, 11.07.

**General Procedure for the Synthesis of Aminophosphite-Terminated Dendrimers 10-[G₁] and 10-[G₅].** To a solution of 0.120 g of dendrimer 1-[G$_n$] ($n = 1$, 0.075 mmol; $n = 5$, 0.0035 mmol) in THF (10 mL) were added chlorodiethylphosphine ($n = 1$, 130 µL, 0.90 mmol; $n = 5$, 98 µL, 0.677 mmol) and triethylamine ($n = 1$, 126 µL, 0.90 mmol; $n = 5$, 100 µL, 0.677 mmol). The resulting mixture was stirred for 2 h at room temperature and then filtered and evaporated to dryness to give a white powder, very sensitive to oxidation.

**10-[G₁]:** white powder; 40% yield (0.070 g); $^{31}$P NMR $\delta$ 52.5, 62.8, 139.2; $^1$H NMR $\delta$ 1.22 (t, $J = 7.0$, 36H), 2.93 (d, $J = 1.0$, 18H), 3.33 (d, $J = 10.4$, 9H), 3.71–3.85 (m, 24H), 7.15–7.77 (m, 45H); $^{13}$C NMR $\delta$ 16.7 (d, $J = 6$), 28.4, 32.9 (d, $J = 13$), 59.7 (d, $J = 17$), 121.4 (d, $J = 4$), 126.9, 128.3, 132.5, 132.6, 133.3 (d, $J = 28$), 138.2 (d, $J = 12$), 149.9 (d, $J = 7$), 150.9 (d, $J = 8$). Anal. Calcd for $C_{96}H_{132}N_{18}O_{21}P_{10}S_4$: C, 49.87; H, 5.75; N, 10.90. Found: C, 49.73; H, 5.71; N, 10.72.

**10-[G₅]:** white powder; 64% yield (0.102 g); $^{31}$P NMR $\delta$ 62.6, 62.7, 138.6; $^1$H NMR $\delta$ 1.15–1.27 (m, 576H), 2.85 (d, $J = 1.87$, 288H), 3.25 (d, $J = 11.6$, 279H), 3.70–3.86 (m, 384H), 7.11–7.60 (m, 945H); $^{13}$C NMR $\delta$ 16.7 (d, $J = 5$), 28.4, 32.9 (d, $J = 12$), 59.6 (d, $J = 17$), 121.3 (d, $J = 3$), 121.6 (d, $J = 6$), 126.9, 128.0, 132.0, 132.6, 133.2 (d, $J = 28$), 138.3–140.0 (m), 149.9 (d, $J = 7$), 151.1 (d, $J = 9$). Anal. Calcd for $C_{1896}H_{2472}N_{378}O_{381}P_{190}S_{94}$: C, 49.99; H, 5.47; N, 11.62. Found: C, 49.76; H, 5.32; N, 11.51.

**Synthesis of Ylide-Terminated Dendrimer 11-[G₁].** To a solution of (triphenylphosphoranylidene)ethenone (0.120 g, 0.397 mmol) in THF (7 mL) was added 9-[G₁] (0.105 g, 0.066 mmol) in THF (5 mL) at room temperature. The resulting mixture was stirred for 24 h at room temperature and then evaporated to dryness. The resulting powder was washed with $3 \times 10$ mL of THF/ether/pentane (1/2/2).

**11-[G₁]:** yellow powder; 78% yield (0.175 g); $^{31}$P NMR $\delta$ 18.3, 52.8, 62.6; $^1$H NMR $\delta$ 3.3 (s, 18H), 3.3 (d, $J = 11.5$, 9H), 4.2 (br d, $J = 25$, 6H), 7.1–7.7 (m, 135H); $^{13}$C NMR $\delta$ 26.8, 32.4 (d, $J = 13$), 32.5 (d, $J = 127$), 120.9 (d, $J = 4$), 126.7, 127.5, 128.0 (d, $J = 12$), 129.7 (d, $J = 13$), 131.1, 132.4 (d, $J = 10$), 133.3, 134.3, 137.5 (d, $J = 14$), 149.6 (d, $J = 7$), 150.4 (d, $J = 8$), 170.3 (d, $J = 12$); IR (KBr) 1663 cm$^{-1}$ ($\nu_{C=O}$). Anal. Calcd for $C_{192}H_{168}N_{18}O_{15}P_{10}S_4$: C, 67.71; H, 4.97; N, 7.40. Found: C, 67.62; H, 4.87; N, 7.01.

**Reaction of Dendrimer 11-[G₁] with Aldehydes.** To a solution of 0.211 mg (0.062 mmol) of dendrimer 11-[G₁] in THF (10 mL) was added benzaldehyde (0.040 mL, 0.37 mmol) or crotonaldehyde (0.031 mL, 0.37 mmol). The resulting mixture was stirred overnight at room temperature (benzaldehyde) or for 1 week at 40 °C (crotonaldehyde). The solvent was evaporated under vacuum to give a yellow powder that was washed with $3 \times 10$ mL of THF/ether/pentane (1/2/2).

**12-[G₁]:** pale yellow powder; 66% yield (0.097 g); $^{31}$P NMR $\delta$ 52.9, 62.2; $^1$H NMR $\delta$ 3.32 (d, $J = 14.1$, 9H), 3.42 (s, 18H), 7.2–7.8 (m, 87H); $^{13}$C NMR $\delta$ 27.3, 27.6, 32.4 (d, $J = 12$), 116.8, 117.0, 121.3 (d, $J = 6$), 121.7 (d, $J = 6$), 127.9, 128.1, 128.3, 128.4, 128.6, 131.9, 132.0, 137.5 (d, $J = 12$), 137.6, 139.2, 142.2, 142.5, 151.0 (d, $J = 9$), 151.3 (d, $J = 7$), 166.3, 167.0. IR (KBr) 1663 cm$^{-1}$ ($\nu_{C=O}$). Anal. Calcd for $C_{126}H_{114}N_{18}O_{15}P_4S_4$: C, 63.79; H, 4.84; N, 10.63. Found: C, 63.52; H, 4.71; N, 10.49.

**13-[G₁]:** pale yellow powder; 63% yield (0.08 g); $^{31}$P NMR $\delta$ 52.9, 62.2; $^1$H NMR (400 MHz, $^2$D) $\delta$ 1.80–1.90 (m, 12H, CH–CHC$H_3$), 3.30–3.40 (m, 27H, P$_1$NCH$_3$, C(O)NCH$_3$), 6.05 (m, $(6 \times 0.1)$H, *cis,trans*-CH$_d$=CH$_c$CH$_b$=C$H_a$Me), 6.13 (dq, $^3J_{HaHb} = 15.1$, $^3J_{HaCH3} = 6.6$ $(6 \times 0.9)$H, *trans,trans*-CH$_d$=CH$_c$CH$_b$=C$H_a$Me), 6.31 (m, $(6 \times 0.9)$H, *trans,trans*-CH$_d$=CH$_c$C$H_b$=CH$_a$Me), 6.54 (m, $(6 \times 0.1)$H, *cis,trans*-CH$_d$=CH$_c$C$H_b$=CH$_a$Me), 6.80 (d, $^3J_{HdHc} = 10.0$, $(6 \times 0.1)$H, *cis,trans*-C$H_d$=CH$_c$CH$_b$=CH$_a$Me), 7.12 (t, $^3J_{HdHc} = 15.0$, $(6 \times 0.9)$H, *trans,trans*-C$H_d$=CH$_c$CH$_b$=CH$_a$Me), 7.37 (dd, $^3J_{HdHc} = 15.0$, $^3J_{HdHc} = 10.1$, $(6 \times 0.9)$H, *trans,trans*-CH$_d$=C$H_c$CH$_b$=CH$_a$Me), 7.20–7.80 (m, 45H, CH=N, C$_6$H$_4$ and *cis,trans*-CH$_d$=C$H_c$CH$_b$=CH$_a$Me); $^{13}$C NMR $\delta$ 18.5, 27.4, 27.9, 32.9 (d, $J = 13$),

114.7, 117.8, 121.4 (d, $J = 4$), 121.6 (d, $J = 5$), 128.0, 128.3, 130.3, 130.4, 132.2, 137.1, 137.2 (d, $J = 11$), 138.2, 138.3, 142.7, 143.6, 151.0 (d, $J = 7$), 151.2 (d, $J = 9$), 166.6, 167.5; IR (KBr) 1663 cm$^{-1}$ ($\nu_{C=O}$). Anal. Calcd for $C_{108}H_{114}N_{18}O_{15}P_4S_4$: C, 60.15; H, 5.33; N, 11.69. Found: C, 59.97; H, 5.27; N, 11.60.

**General Procedure for the Synthesis of Phosphonate-Terminated Dendrimers 14-[G₁]–14-[G₅].** To 0.200 g of dendrimer 1-[G$_n$] ($n = 1$, 0.140 mmol; $n = 2$, 0.058 mmol; $n = 3$, 0.027 mmol; $n = 4$, 0.013 mmol; $n = 5$, 0.0064 mmol) were added triethylamine ($n = 1$, 30 µL; $n = 2$, 50 µL; $n = 3$, 50 µL; $n = 4$, 140 µL; $n = 5$, 140 µL) and diethyl phosphite (the quantity necessary to dissolve 1-[G$_n$]: $n = 1$, 0.6 mL, $n = 2$, 1.0 mL; $n = 3$, 1.0 mL; $n = 4$, 2.9 mL; $n = 5$, 2.9 mL). The mixture was stirred overnight at room temperature and then evaporated under vacuum to give an oil. Addition of ether/pentane precipitated this oil. The resulting powder was washed with acetonitrile.

**14-[G₁]:** white powder; 27% yield (0.085 g); $^{31}$P NMR $\delta$ 21.3 (d, $^7J_{PP} = 3.9$, P(O)), 51.8 (s, P$_0$), 62.0 (t, $^7J_{PP} = 3.9$, P$_1$); $^1$H NMR $\delta$ 1.20 (m, 36H), 3.30 (d, $J = 10.3$, 9H), 3.92 (m, 24H), 4.90 (s, 6H), 4.93 (d, $J = 11.5$, 6H), 7.15–7.73 (m, 39H); $^{13}$C NMR $\delta$ 16.2 (d, $J = 4$), 32.7 (d, $J = 13$), 63.0 (d, $J = 10$), 63.2 (d, $J = 8$), 69.8 (d, $J = 160$), 121.0, 121.3, 128.2, 132.5, 133.8, 138.2 (d, $J = 12$), 150.0 (d, $J = 7$), 150.9 (d, $J = 6$); IR (KBr) 3270 cm$^{-1}$ ($\nu_{OH}$). Anal. Calcd for $C_{90}H_{120}N_6O_{33}P_{10}S_4$: C, 48.00; H, 5.37; N, 3.73. Found: C, 47.81; H, 5.28; N, 3.61.

**14-[G₂]:** white powder; 19% yield (0.079 g); $^{31}$P NMR (CH$_2$Cl$_2$) $\delta$ 20.8 (d, $J = 4.0$), 51.7, 61.4, 61.8 (t, $J = 4.0$); $^1$H NMR (CD$_3$OD) $\delta$ 1.23 (m, 72H), 3.32 (d, $J = 10.3$, 27H), 3.98 (m, 48H), 5.04 (d, $J = 13.0$, 12H), 7.23–7.76 (m, 93H); $^{13}$C NMR (CD$_3$OD) $\delta$ 17.3 (d, $J = 3$), 34.1 (d, $J = 13$), 64.7 (d, $J = 7$), 65.0 (d, $J = 7$), 71.0 (d, $J = 165$), 122.6, 123.3, 129.7, 130.2 (d, $J = 4$), 134.0, 136.3, 141.2 (d, $J = 12$), 151.3, 152.0 (d, $J = 4$); IR (KBr) 3272 cm$^{-1}$ ($\nu_{OH}$). Anal. Calcd for $C_{204}H_{264}N_{18}O_{69}P_{22}S_{10}$: C, 48.32; H, 5.25; N, 4.97. Found: C, 48.27; H, 5.19; N, 4.85.

**14-[G₃]:** white powder; 18% yield (0.052 g); $^{31}$P NMR (CH$_2$Cl$_2$) $\delta$ 21.2 (d, $J = 3.8$), 52.3, 62.2 (br s); $^1$H NMR (CD$_3$OD) $\delta$ 1.21 (m, 144H), 3.22 (m, 63H), 4.00 (m, 96H), 5.03 (d, $J = 12.6$, 24H), 7.23–7.67 (m, 201H); $^{13}$C NMR (CD$_3$OD) $\delta$ 17.3, 34.2 (d, $J = 10$), 64.7 (d, $J = 8$), 65.0 (d, $J = 7$), 71.0 (d, $J = 166$), 122.6, 123.2, 130.3 (m), 134.1, 136.3, 140.5 (m), 151.0, 152.1 (d, $J = 4$); IR (KBr) 3271 cm$^{-1}$ ($\nu_{OH}$). Anal. Calcd for $C_{432}H_{552}N_{42}O_{141}P_{46}S_{22}$: C, 48.40; H, 5.19; N, 5.49. Found: C, 48.23; H, 5.11; N, 5.37.

**14-[G₄]:** white powder; 18% yield (0.052 g); $^{31}$P NMR (CH$_2$Cl$_2$) $\delta$ 21.2 (d, $J = 4.3$), 62.2 (br s); $^1$H NMR (CD$_3$OD): $\delta$ 1.21 (m, 288H), 3.26 (m, 135H), 4.00 (m, 192H), 5.03 (d, $J = 12.7$, 48H), 7.25–7.67 (m, 417H); $^{13}$C NMR (CD$_3$OD) $\delta$ 17.3, 34.0 (m), 64.7 (d, $J = 7$), 65.0 (d, $J = 7$), 71.0 (d, $J = 166$), 122.6, 130.2, 133.7–134.0 (m), 136.3, 140.0–141.5 (m), 152.1 (d, $J = 5$); IR (KBr) 3270 cm$^{-1}$ ($\nu_{OH}$). Anal. Calcd for $C_{888}H_{1128}N_{90}O_{285}P_{94}S_{46}$: C, 48.46; H, 5.16; N, 5.73. Found: C, 48.23; H, 5.03; N, 5.61.

**14-[G₅]:** white powder; 22% yield (0.059 g); $^{31}$P NMR (CH$_2$Cl$_2$) $\delta$ 21.3 (d, $J = 4.5$), 62.4 (br s); $^1$H NMR (CD$_3$OD) $\delta$ 1.20 (m, 576H), 3.25 (m, 279H), 4.05 (m, 384H), 5.03 (d, $J = 13.2$, 96H), 7.23–7.67 (m, 849H); $^{13}$C NMR (CD$_3$OD) $\delta$ 17.3, 34.0 (m), 64.7 (d, $J = 7$), 65.0 (d, $J = 7$), 71.0 (d, $J = 166$), 122.6, 130.2, 133.8–134.1 (m), 136.3, 140.0–141.0 (m), 151.0, 152.1; IR (KBr) 3270 cm$^{-1}$ ($\nu_{OH}$). Anal. Calcd for $C_{1800}H_{2280}N_{186}O_{573}P_{190}S_{94}$: C, 48.48; H, 5.15; N, 5.84. Found: C, 48.51; H, 5.09; N, 5.78.

**General Procedure for the Synthesis of Phosphonate-Terminated Dendrimers 15-[G₁] and 15-[G₅].** To 0.200 g of dendrimer 1-[G$_n$] ($n = 1$, 0.140 mmol; $n = 5$, 0.0064 mmol) were added dilauryl phosphite ($n = 1$, 0.775 mL, 1.68 mmol; $n = 5$, 0.682 mL, 1.5 mmol) and then triethylamine ($n = 1$, 20 µL; $n = 5$, 100 µL). The resulting mixture was stirred for 3 days at room temperature (for 15-[G₁]) or for 5 days at room temperature then for 2 days at 45 °C (for 15-[G₅]). Evaporation under vacuum gave an oil that was washed several times with acetonitrile to give a white powder.

**15-[G₁]:** white powder; 16% yield (0.089 g); $^{31}$P NMR $\delta$ 21.2 (d, $J = 3.8$), 51.8, 62.2 (t, $^7J = 3.8$); $^1$H NMR $\delta$ 0.85 (t, $J = 5.0$, 36H), 1.22 (br s, 216 H), 1.40–1.55 (m, 24H), 3.30 (d, $J = 9.8$,

9H), 3.80–3.95 (m, 24H), 4.60 (br s, 6H), 4.95 (d, $J$ = 6.5, 6H), 7.16–7.74 (m, 39H); $^{13}$C NMR $\delta$ 13.9, 22.5, 25.2, 28.9, 29.2, 29.4, 29.5, 30.3, 30.4, 31.7, 32.9 (d, $J$ = 12), 66.9 (d, $J$ = 8), 67.2 (d, $J$ = 7), 70.0 (d, $J$ = 159), 121.0, 121.4, 128.2, 132.5, 133.7, 137.9, 150.0, 151.0 (d, $J$ = 9); IR (KBr) 3270 cm$^{-1}$ ($\nu_{OH}$). Anal. Calcd for $C_{210}H_{360}N_6O_{33}P_{10}S_4$: C, 64.10; H, 9.22; N, 2.14. Found: C, 64.25; H, 9.34; N, 2.07.

**15-[G₅]:** white powder; 27% yield (0.123 g); $^{31}$P NMR $\delta$ 21.3, 62.6 (m); $^{1}$H NMR $\delta$ 0.84 (br s, 576H), 1.21 (br s, 3456H), 1.50 (br s, 384H), 2.87 (br s, 96H), 3.27 (br s, 279H), 3.90 (br s, 384H), 4.95 (br s, 96H), 7.17–7.65 (m, 849H); $^{13}$C NMR $\delta$ 13.9, 22.5, 25.2, 28.9, 29.2, 29.5, 30.3, 31.7, 32.5 (m), 66.5 (d, $J$ = 7), 67.1 (d, $J$ = 7), 71.3, 121.0, 121.7, 128.1, 132.0, 133.9, 137.6–139.4 (m), 149.9 (d, $J$ = 7), 151.2 (d, $J$ = 7); IR (KBr) 3270 cm$^{-1}$ ($\nu_{OH}$). Anal. Calcd for $C_{3720}H_{6120}N_{186}O_{573}P_{190}S_{94}$: C, 62.47; H, 8.62; N, 3.64. Found: C, 62.73; H, 8.80; N, 3.52.

**Synthesis of Dendrimer 16-[G₁].** To 0.300 g (0.33 mmol) of (S)P[OC₆H₄CH=NN(Me)P(S)Cl₂]₃[2] in THF (30 mL) was added 0.420 g (2.27 mmol) of 4-hydroxy-3-methoxycinnamaldehyde sodium salt. The resulting mixture was stirred for 5 days at 40 °C and then centrifuged. The solution was evaporated to dryness to give a powder that was washed twice with pentane/ether (1/1).

**16-[G₁]:** yellow powder; 48% yield (0.278 g); $^{31}$P NMR $\delta$ 52.7, 62.0; $^{1}$H NMR $\delta$ 3.40 (d, $J$ = 9.9, 9H), 3.73 (s, 18H), 6.51 (dd, $J$ = 16.0, 7.0, 6H), 7.00–7.34 (m, 33H), 7.55 (d, $J$ = 16.0, 6H), 9.54 (d, $J$ = 7.0, 6H); $^{13}$C NMR $\delta$ 32.5 (d, $J$ = 12), 55.9, 111.7, 121.1, 121.5, 122.3, 128.2, 131.7, 132.6, 137.9 (d, $J$ = 15), 142.3 (d, $J$ = 8), 150.6 (d, $J$ = 8), 151.3 (d, $J$ = 6), 151.9, 193.4; IR (KBr) 1677 cm$^{-1}$ ($\nu_{CHO}$). Anal. Calcd for $C_{84}H_{78}N_6O_{21}P_4S_4$: C, 57.33; H, 4.47; N, 4.78. Found: C, 57.18; H, 5.48; N, 4.71.

**Synthesis of Phosphonate-Terminated Dendrimer 17-[G₁].** To 0.280 g (0.160 mmol) of dendrimer 16-[G₁] were added triethylamine (30 µL) and diethyl phosphite (the quantity necessary to dissolve 16-[G₁]: 0.5 mL). The mixture was stirred overnight at room temperature and then evaporated under vacuum to give an oil that was washed with acetonitrile to give a powder.

**17-[G₁]:** yellow powder; 18% yield (0.074 g); $^{31}$P NMR $\delta$ 21.3, 52.3, 62.1; $^{1}$H NMR $\delta$ 1.28 (m, 36H), 2.62 (br s, 6H), 3.40 (d, $J$ = 10.0, 9H), 3.75 (s, 18H), 4.13 (m, 24H), 4.61 (dd, $J$ = 13.4, 5.0, 6H), 6.21 (d, $J$ = 15.7, 6H), 6.67 (dd, $J$ = 15.7, 5.0, 6H), 6.86–7.67 (m, 33H, C₆H₄); $^{13}$C NMR $\delta$ 16.5 (d, $J$ = 6), 32.7 (d, $J$ = 12), 56.0, 63.2 (d, $J$ = 6), 69.3 (d, $J$ = 162), 110.7, 119.1, 121.3, 122.2, 124.1, 128.3, 133.0, 134.3, 137.4 (d, $J$ = 16), 139.9, 150.8 (d, $J$ = 8), 151.2, (d, $J$ = 6); IR (KBr) 3270 cm$^{-1}$ ($\nu_{OH}$). Anal. Calcd for $C_{108}H_{144}N_6O_{39}P_{10}S_4$: C, 50.12; H, 5.61; N, 3.25. Found: C, 50.01; H, 5.49; N. 3.21.

**General Procedure for the Synthesis of Imine-Terminated Dendrimers 18-[G₁] and 18-[G₅].** To a solution of 0.250 g of 1-[Gₙ] ($n$ = 1, 0.176 mmol; $n$ = 5, 0.008 mmol) in THF (10 mL) was added propylamine ($n$ = 1, 0.180 mL, 2.112 mmol; $n$ = 5, 0.130 mL, 1.530 mmol) in the presence of molecular sieves (4 Å). The mixture was stirred at room

temperature for 24 h and then filtered and evaporated to dryness. The resulting powder was washed with ether.

**18-[G₁]:** white powder; 61% yield (0.179 g); $^{31}$P NMR $\delta$ 52.4, 61.9; $^{1}$H NMR $\delta$ 0.90 (t, $J$ = 6.7, 18H), 1.67 (m, 12H), 3.35 (d, $J$ = 10, 9H), 3.51 (m, 12H), 7.26–7.70 (m, 39H), 8.20 (s, 6H); $^{13}$C NMR $\delta$ 11.7, 23.8, 32.9 (d, $J$ = 14), 63.2, 121.4, (d, $J$ = 4), 128.3, 129.2, 132.4, 133.5, 138.4 (d, $J$ = 14), 151.0 (d, $J$ = 7), 152.0 (d, $J$ = 9), 159.3; IR (KBr) 1647 cm$^{-1}$ ($\nu_{C=N}$). Anal. Calcd for $C_{84}H_{96}N_{12}O_9P_4S_4$: C, 60.42; H, 5.79; N, 10.06. Found: C, 60.31; H, 5.67; N, 9.95.

**18-[G₅]:** white powder; 46% yield (0.130 g); $^{31}$P NMR $\delta$ 61.9, 62.5; $^{1}$H NMR $\delta$ 0.86 (br s, 288H), 1.61 (br s, 192H), 3.28 (br s, 279H), 3.47 (br s, 192H), 7.21–7.65 (m, 849H), 8.15 (s, 96H); $^{13}$C NMR $\delta$ 11.7, 23.8, 32.8 (m), 63.2, 121.4 (d, $J$ = 4), 121.7, 128.1, 129.1, 131.9, 133.5, 138–139 (m), 151.2 (d, $J$ = 5), 151.9 (d, $J$ = 6), 159.3; IR (KBr) 1647 cm$^{-1}$ ($\nu_{C=N}$). Anal. Calcd for $C_{1704}H_{1896}N_{282}O_{189}P_{94}S_{94}$: C, 58.01; H, 5.42; N, 11.20. Found: C, 57.88; H, 5.33; N, 11.06.

**General Procedure for the Synthesis of Phosphonate-Terminated Dendrimers 19-[G₁] and 19-[G₅].** To 0.130 g of dendrimer 18-[Gₙ] ($n$ = 1, 0.078 mmol; $n$ = 5, 0.0037 mmol) was added diethyl phosphite (the quantity necessary to dissolve 18-[Gₙ]: $n$ = 1, 0.6 mL; $n$ = 5, 2.0 mL) and then triethylamine ($n$ = 1, 30 µL; $n$ = 5, 150 µL). This mixture was stirred overnight at room temperature and then evaporated to dryness. Dendrimer 19-[G₁] was purified by extraction with pentane/toluene. Dendrimer 19-[G₅] was purified by washings with pentane, ether, and then acetonitrile.

**19-[G₁]:** white powder; 11% yield (0.022 g); $^{31}$P NMR $\delta$ 23.5 (d, $J$= 4.5), 52.6, 62.5 (t, $J$ = 4.5); $^{1}$H NMR $\delta$ 0.83 (t, $J$ = 7.3, 18H), 1.08 (t, $J$ = 7.0, 18H), 1.21 (t, $J$ = 7.0, 18H), 1.40 (m, 12H), 2.11 (s, 6H), 2.41 (m, 12H), 3.34 (d, $J$ = 10.4, 9H), 3.70–4.08 (m, 30H), 7.15–7.77 (m, 39H); $^{13}$C NMR $\delta$ 11.5, 16.1 (d, $J$ = 7), 16.2 (d, $J$ = 6), 22.7, 32.8, (d, $J$ = 13), 49.7 (d, $J$ = 16), 60.2 (d, $J$ = 153), 62.6 (d, $J$ = 7), 62.8 (d, $J$ = 8), 121.1 (d, $J$ = 3), 121.4, 128.2, 129.4 (d, $J$ = 6), 132.5, 133.0 (d, $J$ = 4), 138.2 (d, $J$ = 15), 149.9 (d, $J$ = 7), 150.9 (d, $J$ = 8); IR (KBr) 3300 cm$^{-1}$ ($\nu_{NH}$). Anal. Calcd for $C_{108}H_{162}N_{12}O_{27}P_{10}S_4$: C, 51.92; H, 6.53; N, 6.73. Found: C, 51.80; H, 6.50; N, 6.62.

**19-[G₅]:** white powder; 24% yield (0.043 g); $^{31}$P NMR $\delta$ 22.9 (d, $J$ = 4.5), 62.1; $^{1}$H NMR $\delta$ 0.77 (br s, 288H), 1.03 (br s, 288H), 1.18 (br s, 288H), 1.45 (br s, 192H), 2.3–2.4 (m, 288H), 3.30 (br s, 279H), 3.85–4.00 (m, 480H), 7.15–7.65 (m, 849H); $^{13}$C NMR $\delta$ 11.4, 16.0 (d, $J$ = 5), 16.2 (d, $J$ = 5), 21.2–22.0 (m), 32.6–33.0 (m), 49.3–49.5 (m), 59.5 (d, $J$ = 160), 62.9 (m), 121.2–121.6 (m), 128.0, 129.7, 131.5–131.9 (m), 138.1–139.1 (m), 150.1–150.3 (m), 151.1; IR (KBr) 3300 cm$^{-1}$ ($\nu_{NH}$). Anal. Calcd for $C_{2088}H_{2952}N_{282}O_{477}P_{190}S_{94}$: C, 51.67; H, 6.13; N, 8.14. Found: C, 51.32; H, 6.05; N, 8.06.

# Application of the Horner-Wadsworth-Emmons Reaction to the Functionalization of Dendrimers: Synthesis of Amino Acid Terminated Dendrimers

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**Abstract:**

The Horner-Wadsworth-Emmons reaction of the first, third and fourth generation of aldehyde terminated dendrimers **1-[Gn]** (**n** = 1: 6 CHO, **n** = 3: 24 CHO, **n** = 4: 48 CHO groups, respectively) with phosphonates unsubstituted at the carbon $\alpha$ to the phosphoryl group **2a-i** affords in moderate yield dendrimers bearing various $\alpha,\beta$-unsaturated functional groups on the surface, including amino acid derivatives.

**Key words:** Dendrimer, arborol, phosphonate, Horner-Wadsworth-Emmons reaction, amino-acid

The design of highly branched macromolecules with well defined structure and constitution, namely dendrimers[1] gives rise to an increasing interest in several fields of chemistry, including biochemistry. For instance, natural amino acids have been included several times in the skeleton of dendritic structures, or grafted on the surface. In previous examples, amino acids such as $\alpha,\omega$-diamino carboxylic acids (mainly lysine) were used as building blocks in divergent syntheses up to the tenth generation.[2] Later, oligonucleotides were used in convergent syntheses.[3] Small lysine dendrimers have also been a support for the grafting of peptides,[4] carboranes and peptides,[5] or $\alpha$-thiosialosides[6] onto the surface, whereas poly(ethylene oxide) has been grafted to the core.[7] Several antibodies have also been linked to the surface of organic dendrimers such as PAMAM dendrimers.[8]

All the above-mentioned papers deals with the use of "oligomeric" amino acids; in contrast, only one series of reports concerns the synthesis of dendrimers possessing monomeric amino acids on the surface. They were obtained by the modification of poly (propylene imine) dendrimer end-groups with bulky amino acids, which resulted in a "dendritic box" able to encapsulate small molecules.[9] We recently described the synthesis of phosphorus containing dendrimers possessing either $PCl_2$ or aldehyde end-groups[10] and the grafting on the surface of various types of functional groups.[11] Pursuing our investigations in the field of functionalized dendrimers, it appeared interesting to try to graft natural amino acids onto the surface. Amino acid could be grafted directly by a Schiff reaction with the aldehyde end-groups, but the resulting imine bonds would be too sensitive to hydrolysis. In order to get amino acids firmly bounded to the dendrimers, we decided to use the Horner-Wadsworth-Emmons reaction[12] which creates a carbon carbon double bond, starting from the phosphonylated amino acids of general formula $(EtO)_2P(O)CH_2C(S)$[amino acid] that we recently described.[13]

To demonstrate the versatility of the Horner-Wadsworth-Emmons reaction applied to dendrimers, we carried out preliminary experiments with the first ($1$-$[G_1]$), third ($1$-$[G_3]$), or fourth ($1$-$[G_4]$) generation of the dendrimer (6, 24, or 48 aldehyde end-groups, respectively) and with the salts of the ester, phosphonate, thioamide, and carboxylic acid derivatives of phosphonates $2a$-$e$. Subsequent reactions were carried out with the salts of the amino acid derivatives of phosphonates $2f$-$i$. Two different synthetic procedures have been applied,

depending on the absence or presence of carboxylic acid on compounds **2**. In the former case, one equivalent of sodium hydride is added to the phosphonates **2a-d** to afford the corresponding phosphonate salts. Then, the dendrimer is added to this salt, used *in situ* and stirred overnight. All these experiments are carried out with the first generation of the dendrimer **1-[G$_1$]** (Scheme 1). This procedure affords dendrimers **3a-[G$_1$]** − **3d-[G$_1$]** in quantitative yield as crude products, and in moderate yield after workup (see Table 1).

All these compounds have been characterized by $^{31}$P, $^1$H, and $^{13}$C NMR (Table 1), IR, and elemental analyses. The reaction induces a slight deshielding of the signal corresponding to the external phosphorus (P$_1$) of the dendrimer, from 60.1 ppm for **1-[G$_1$]** to 60.9-61.4 ppm for **3a-[G$_1$]** − **3d-[G$_1$]**. Furthermore, the formation of the carbon carbon double bond is unambiguously proved by the total disappearance of the aldehyde signals on $^1$H and $^{13}$C NMR, and IR spectra, and by the appearance of new signals corresponding to the HC=CH linkage. Indeed, two new doublets appears in the $^1$H NMR spectrum of compound **3a-[G$_1$]** at δ = 6.34 and 7.61 ppm ($^3J_{HH}$ = 16 Hz), corresponding to CH=C$\underline{H}$-CO and C$\underline{H}$=CH-CO, respectively. The value of the coupling constant indicates a *E*-configuration for all the HC=CH linkages. The formation of the alkene moieties is also confirmed by the $^{13}$C NMR spectrum, with the appearance of two singlets at δ = 118.4 (CH=$\underline{C}$H-CO) and 143.3 ppm ($\underline{C}$H=CH-CO). A similar trend is observed for dendrimer **3b-[G$_1$]** which possesses six unsaturated phosphonate functions. In this case, the $^1$H NMR spectrum is slightly complicated by the presence of the phosphonate moieties. Indeed, the signal corresponding to CH=C$\underline{H}$-P(O) appears as a doublet of doublet, with two equivalent coupling constants (δ = 6.15 ppm, $^2J_{HP}$ = $^3J_{HH}$ = 17.3 Hz), whereas the signal corresponding to C$\underline{H}$=CH-P(O) appears as a single doublet (δ = 7.47 ppm, $^3J_{HH}$ = 17.3 Hz). The formation of the carbon carbon double bond is also demonstrated by the presence of two doublets in the $^{13}$C NMR spectrum at δ = 113.9 ppm ($^1J_{CP}$ = 191 Hz) for CH=$\underline{C}$H-P(O) and δ = 147.3 ppm ($^2J_{CP}$ = 7 Hz) for $\underline{C}$H=CH-P(O).

The above mentioned data indicate for both compounds **3a-[G$_1$]** and **3b-[G$_1$]** the unique formation of the *E* isomer of the double bond. A different behaviour is observed for compounds **3c-[G$_1$]** and **3d-[G$_1$]**. Indeed, beside the expected signals corresponding to the *E* isomers, several other signals appear in the $^1$H and $^{13}$C NMR spectra of both compounds, as already

observed in some cases for alkene bonds obtained by Wittig reactions on dendrimers.[11c] For example, the ^{1}H NMR spectrum of 3c-[G$_1$] displays a AB system at $\delta$ = 6.20 and 6.26 ppm, with $^3J_{HH}$ = 12.0 Hz. The smaller value of the coupling constant and the shielding of the signals indicate the formation of the Z isomer.[13] Integration of these signals compared to that of the E isomer gives approximately 10/90 for the Z/E ratio. Both isomers are also detected on the ^{13}C NMR spectrum of 3c-[G$_1$]. The signal corresponding to the Z isomer appears at higher field than for the E isomer ($\delta$ = 124.9 and 126.0 ppm for Z and E CH=CH-C(S), respectively; $\delta$ = 128.0 and 140.4 ppm for Z and E CH=CH-C(S), respectively). The same behaviour is observed for dendrimer 3d-[G$_1$]. In this case, integration of the Z and E signals of the alkene bond in ^{1}H NMR indicates the formation of a higher proportion of Z isomer (30/70 for the Z/E ratio). Obviously, isomers of compounds 3c-[G$_1$] and 3d-[G$_1$] cannot be purified, as both E and Z isomers are linked to the same dendrimer.

All these experiments have been extended to the third 1-[G$_3$] or fourth 1-[G$_4$] generation of the dendrimer which possesses 24 or 48 aldehyde end groups (Scheme 2, Figure 1). These reactions are slightly slower than for the first generation and need two days at room temperature to go to completion. The reactions are monitored by ^{31}P NMR which indicates the total disappearance of the signal of the external phosphorus (P$_3$: $\delta$ = 60.1 ppm for 1-[G$_3$]; P$_4$: $\delta$ = 60.0 ppm for 1-[G$_4$]) on behalf of a new singlet slightly deshielded (P$_3$: $\delta$ = 60.9 ppm for 3d-[G$_3$]; P$_4$: $\delta$ = 61.0-61.4 ppm for 3a-[G$_4$] – 3c-[G$_4$]). The reaction of all the aldehyde groups is confirmed by ^{1}H and ^{13}C NMR, and IR spectra with the total disappearance of the signals corresponding to these linkages. Furthermore, beside the signals corresponding to the skeleton of the dendrimer, ^{1}H and ^{13}C NMR spectra display signals characteristic of the CH=CH-R moieties, as already seen for the first generation (Table 1). Dendrimers 3a-[G$_4$] and 3b-[G$_4$] possess a all-E configuration, as noted for 3a-[G$_1$] and 3b-[G$_1$], whereas a mixture of E and Z configuration is observed for 3c-[G$_4$] and 3d-[G$_3$]. The Z/E ratio seems to depend on the generation used for compounds 3d (Z/E $\cong$ 30/70 for 3d-[G$_1$]; 50/50 for 3d-[G$_3$]) but not for compounds 3c (Z/E $\cong$ 10/90 for 3c-[G$_1$] and 3c-[G$_4$]). It must be noted that the precision of the technique used, ^{1}H NMR, is hampered by the occurrence of signals of

the $E$ CH=CH linkage within the area corresponding to the $C_6H_4$ and CH=N signals of the dendrimer skeleton.

After these preliminary experiments, we have tried to apply the same procedures to phosphonates bearing acid or amino acid substituents **2e-i**. In these cases, two equivalents of base are required: one reacts with the carboxylic acid, the other creates the carbanion $\alpha$ to the phosphonate. A first attempt was carried out with phosphonate **2f** (glycine derivative) and two equivalents of sodium hydride. The reaction with the first generation is slow and necessitates to be heated. In this case, the monitoring by $^{31}P$ NMR indicates the partial cleavage of the skeleton of the dendrimer, thus compound **3f-[G₁]** is extremely difficult to isolate in these conditions. We encountered analogous problems with the salt of phosphonate **2g** (alanine derivative) obtained by reaction with one equivalent of triethylamine, and one equivalent of sodium hydride. To overcome these problems, we decided to use two equivalents of butyllithium, which should give a more reactive carbanion. The reaction is carried out first with dendrimer **1-[G₁]** and the simplest acid derivative of phosphonate **2e** in tetrahydrofurane (Scheme 3). A yellow precipitate is observed when the reaction has gone to completion, and no phosphorus derivative remains in solution. The precipitate is solubilized in water and checked by $^{31}P$ NMR. It contains the water soluble dendrimer with six CH=CH-COOLi end groups, and $(EtO)_2P(O)OLi$. In order to separate the dendrimer from $(EtO)_2P(O)OLi$, formic acid is slowly added. A precipitate appears rapidly, and the mixture is acidified up to pH = 3-4. This value allows to maximize the amount of dendrimer **3e-[G₁]** which precipitates; lower pH values precipitates also $(EtO)_2P(O)OH$ and induces the cleavage of the skeleton of the dendrimer. Compound **3e-[G₁]** thus obtained is soluble in several organic solvents such as tetrahydrofuran. This compound is characterized by all the techniques already used for the other dendrimers, and particularly by $^1H$ NMR, which indicates the formation of only one isomer for all the CH=CH bonds. The value of the chemical shift (two doublets at $\delta$ = 6.56 and 7.74 ppm) and the value of the coupling constant ($^3J_{HH}$ = 16 Hz) correspond to the $E$ isomer.

The use of two equivalents of butyl lithium has been extended then to the reaction involving the phosphonate derivatives of glycine (**2f**), L-alanine (**2g**), L-phenylalanine (**2h**), L-methionine

(2i), and dendrimer **1-[G$_1$]** (Scheme 3). In all cases, water soluble dendrimers with HC=CHC(S)NHCHR'COOLi end groups (R' = H, Me, CH$_2$Ph, CH$_2$CH$_2$SMe) are obtained but not isolated, then acidified to give in moderate yields dendrimers **3f-[G$_1$]** – **3i-[G$_1$]**. These dendrimers which possess six HC=CHC(S)NHCHR'COOH end groups are soluble in THF. $^1$H and $^{13}$C NMR spectra of compounds **3f-[G$_1$]** – **3i-[G$_1$]** indicate in all cases the formation of both *E* and *Z* isomers of the carbon carbon double bonds. The presence of isomers is also detected on the level of N-H groups. The *Z/E* ratio, measured by integration of $^1$H NMR spectra, is similar in all cases, roughly 10/90 (see Table 1 and Scheme 3). These compounds are stable in solution or as powders, provided the solvent is not totally eliminated. Indeed, the total removal of last traces of solvents causes the dendrimer to become impossible to solubilize again in organic solvents or in water. This phenomenon, which has not been observed for dendrimers **3a-e**, is presumably due to the formation of inter- and intra-molecular hydrogen bonds between NH and COOH groups.

The extension of the reaction to the third and fourth generation of the dendrimer has been carried out with the dilithium salts of phosphonates **2e-i** in THF (Scheme 3). The dendrimer precipitates very often before the reaction has gone to completion. This can be seen easily when a sample of this precipitate is dissolved in water and checked by $^{31}$P NMR. Beside the signal at $\delta$ = 61.0-61.4 ppm, corresponding to the phosphorus of the external layer (P$_3$ or P$_4$) linked to two OC$_6$H$_4$CH=CHC(S)NHCR'COOLi moieties, another singlet at $\delta$ = 60.5 ppm, corresponding to the external phosphorus linked to one OC$_6$H$_4$CHO and one OC$_6$H$_4$CH=CHC(S)NHCR'COOLi moieties is observed. However, the reaction can be continued in heterogeneous conditions. In these conditions, the reaction rate is slower, but nevertheless the reaction goes to completion after several days. A work up similar to the one used for the first generation allows to isolate dendrimers **3e-[G$_3$]**, **3f-[G$_4$]**, **3g-[G$_3$]**, **3h-[G$_4$]**, and **3i-[G$_4$]** (Figure 1). The absence of any signal corresponding to the CHO groups in $^1$H and $^{13}$C NMR, as well as in IR spectra confirms that all the branches of the dendrimer have reacted. $^1$H NMR spectra indicate the formation of both *E* and *Z* isomers of the CH=CH bond for all the dendrimers having thioamide functions. A higher proportion of *Z* isomer is generally observed for the third and fourth generation than for the first generation (compare *Z/E* = 15/85

for **3g-[G$_3$]**, **3i-[G$_4$]**, and 35/65 for **3f-[G$_4$]**, **3h-[G$_4$]**, to $Z/E$ = 10/90 for **3f-[G$_1$] – 3i-[G$_1$]**).

The reasons of the variations observed for the $Z/E$ ratio, particularly for the amino acid derivatives which differ only by one substituent in $\gamma$ position relative to the reactive site (compounds **2f-i**) are not fully understood. One may presume that steric crowding plays a role, as the $Z$ proportion increases in most cases with the generation. Electronic effects also influence the $Z/E$ ratio, as $Z$ isomers are observed only when thioamide substituents are linked to the phosphonate (compounds **2c-d**, **2f-i**). Furthermore, the nature of the base used to generate the phosphonate salt is also an important factor. Indeed, the $Z/E$ ratio measured for dendrimer **3g-[G$_1$]** generated from the reaction of **2g** with one equivalent of triethylamine and one equivalent of sodium hydride is 30/70, whereas the $Z/E$ ratio measured for the same dendrimer generated from the reaction of **2g** with two equivalents of butyllithium is 10/90.

The presence of chiral amino acids on the surface of dendrimers could have induced interesting optical rotation properties, as we have already shown for dendrimers terminated with chiral methyl benzyl amine.[14] Unfortunately, the formation of both $E$ and $Z$ isomers of the double bond for compounds **3f-[G$_n$] – 3i-[G$_n$]** precludes any study in this field. However, this paper demonstrates that the use of the Horner-Wadsworth-Emmons reaction constitutes a new way of grafting various functional groups on the surface of dendrimers.

## Experimental Section

### General

All manipulations were carried out with standard high vacuum or dry argon atmosphere techniques. $^1$H, $^{31}$P and $^{13}$C NMR spectra were recorded on Bruker AC 80 and AC 200 spectrometers. $^{31}$P NMR chemical shifts are reported in ppm relative to 85% H$_3$PO$_4$. The numbering used for NMR is depicted on Scheme 4. Dendrimers **1-[G1] – 1-[G4]**[10] and phosphonates **2c,2d,2f-2i**[13] are synthesized according to published procedures. Phosphonates **2a**, **2b**, **2e** are purchased from Aldrich. Satisfactory elemental analyses were obtained for all new compounds.

*General procedure for the synthesis of dendrimers 3a-[G₁] – 3d-[G₁], 3d-[G₃], and 3a-[G₄] – 3c-[G₄]:*

To a solution of phosphonate **2a-d** (0.420 mmol) in THF (5 mL) was added NaH (0.420 mmol, 10 mg). The resulting mixture was stirred for 30 min. at room temperature. After evolution of $H_2$, a solution of dendrimer **3-[Gₙ]** (n = 1, 0.070 mmol, 100 mg; **n** = 3, 0.0175 mmol, 130 mg; **n** = 4, 0.00875 mmol, 135 mg) in THF (5 mL) was added to the solution of the phosphonate salt at room temperature and stirred overnight (**1-[G₁]**) or for two days (**1-[G₃]**, **1-[G₄]**), then the solution was evaporated to dryness. The resulting powder was washed with water to eliminate $(EtO)_2P(O)ONa$ and to afford compounds **3a-[G₁]**, **3b-[G₁]**, **3a-[G₄]**, and **3b-[G₄]** which were obtained as white powders. Compounds **3c-[G₁]**, **3d-[G₁]**, **3c-[G₄]**, and **3d-[G₃]** were recovered as yellow powders after purification by column chromatography on silica gel (eluent THF).

*General procedure for the synthesis of dendrimers with carboxylic acid end groups 3e-[G₁] – 3i-[G₁], 3e-[G₃], 3g-[G₃], 3f-[G₄], 3h-[G₄], and 3i-[G₄]:*

To a solution of phosphonate (0.420 mmol) in THF (5 mL) were added 2 equivalents of butyllithium 1.6 M (0.840 mmol, 530 μL) at - 60°C. The resulting solution was stirred for 30 min. at this temperature. A solution of dendrimer **1-[Gₙ]** (n = 1, 0.070 mmol, 100 mg; **n** = 3, 0.0175 mmol, 130 mg; **n** = 4, 0.00875 mmol, 135 mg) in THF (5 mL) was added to the solution of the phosphonate salt at this temperature, then the mixture was allowed to warm up to room temperature and stirred overnight (**1-[G₁]**) or for two days (**1-[G₃]**, **1-[G₄]**). A yellow precipitate appeared. A small sample of the precipitate was dissolved in water and checked by $^{31}P$ NMR. If only one signal appeared for the phosphorus of the external layer ($P_1$ for [**G₁**], $P_3$ for [**G₃**], $P_4$ for [**G₄**]), all the precipitate was isolated by centrifugation and dissolved in water. If two signals appeared for the phosphorus of the external layer, the reaction has not gone to completion. In this case, the sample was thrown away and a small amount of butyllithium (10 % of the initial quantity) was added to the heterogeneous mixture, which was stirred for two days more. Then, another small sample of the precipitate was taken, dissolved in water and

checked by $^{31}$P NMR, to verify that the reaction has gone to completion. The precipitate was then isolated by centrifugation and dissolved in water. In all cases, formic acid was added dropwise to lower the pH from 9 to 3-4 (the use of more acidic conditions induced the cleavage of the dendrimer). A yellow precipitate appeared at acidic pH; it was recovered by centrifugation. This precipitate was then washed with ether and afforded dendrimers **3e-[G$_1$] – 3i-[G$_1$], 3e-[G$_3$], 3f-[G$_4$], 3g-[G$_3$], 3h-[G$_4$]**, and **3i-[G$_4$]** as yellow powders.

## References

(1)    For reviews on dendrimers see for example : (a) Tomalia, D. A.; Naylor, A. M.; Goddart III, W. A. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 138.

(b) Tomalia, D. A.; Durst, H. D. in *Topics in Current Chemistry*, Vol. 165, Weber, E. Ed.; Springer Verlag: Berlin, Heidelberg, **1993**; p 193.

(c) Issberner, J.; Moors, R.; Vögtle, F. *Angew. Chem.* **1994**, *106*, 2507; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2413.

(d) Moorefield, C. N.; Newkome, G. R. in *Advances in Dendritic Molecules*, Vol. 1, Newkome, G. R. Ed.; JAI Press: Greenwich CT, USA **1994**, p 1.

(e) Caminade, A.-M.; Majoral, J.-P. *Main Group Chemistry News* **1995**, 3, 14.

(f) Ardoin, N.; Astruc, D. *Bull. Soc. Chim. Fr.* **1995**, *132*, 876.

(g) Majoral, J.-P.; Caminade, A.-M. *Act. Chim.* **1996**, *4*, 13.

(h) Fréchet, J. M. J.; Hawker, C. J. in *Comprehensive Polymer Science*, 2nd suppl., **1996**, chap. 3, pp 71.

(i) Newkome, G.R.; Moorefield, C.N.; Vögtle, F. in *Dendritic Molecules*, VCH, Weinheim, **1996**

(2)    (a) Denkewalter, R. G.; Kolc, J. F.; Lukasavage, W. J.; *C. A.* **1984**, 100, 103907p (US patent 4,410,688).

(b) Denkewalter, R. G.; Kolc, J.; Lukasavage, W. J. *C. A.* **1985**, 102, 79324q (US patent 4,289,872).

(3)  Hudson, R. H. E., Damha, M. J., *J. Am. Chem. Soc.* **1993**, 115, 2119.

(4)  (a) Posnett, D. N.; McGrath, H.; Tam, J. P. *J. Biol. Chem.* **1988**, 263, 1719.

(b) Rao, C.; Tam, J. P. *J. Am. Chem. Soc.* **1994**, 116, 6975.

(c) Shao, J.; Tam, J. P. *J. Am. Chem. Soc.* **1995**, 117, 14.

(d) Zhang, L.; Tam, J. P. *J. Am. Chem. Soc.* **1997**, 119, 2363.

(5)  Qualmann, B.; Kessels, M. M.; Musiol, H. J.; Sierralta, W. D.; Jungblut, P. W.; Moroder, L. *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 909.

(6)  Roy, R.; Zanini, D.; Meunier, S. J.; Romanowska, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1869.

(7)  Chapman, T. M.; Hillyer, G. L.; Mahan, E. J.; Shaffer, K. A. *J. Am. Chem. Soc.* **1994**, 116, 11195.

(8)  (a) Barth, R. F.; Adams, D. M.; Soloway, A. H.; Alam, F.; Darby, M. V. *Bioconjgate Chem.* **1994**, 5, 58.

(b) Capala, J.; Barth, R. F.; Bendayan, M.; Lauzon, M.; Adams, D. M.; Soloway, A. H.; Fenstermaker, R. A.; Carlsson, J. *Bioconjugate Chem.* **1996**, 7, 7.

(9)  (a) Jansen, J. F. G. A.; de Brabander-van den Berg, E. M. M.; Meijer, E. W. *Science* **1994**, 266, 1226.

(b) Jansen, J. F. G. A.; Peerlings, H. W. I.; de Brabander-van den Berg, E. M. M., Meijer, E. W. *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 1206.

(c) Jansen, J. F. G. A.; Meijer, E. W.; de Brabander-van den Berg, E. M. M. *J. Am. Chem. Soc.* **1995**, 117, 4417.

(d) Jansen, J. F .G. A.; Jansen, R. A. J.; de Brabander-van den Berg, E. M. M.; Meijer, E. W. *Adv. Mater.* **1995**, 7, 561.

(e) Stevelmans, S.; Van Hest, J. C. M.; Jansen, J. F. G. A.; Van Boxtel, D. A. F. J.; de Brabander-van den Berg, E. M. M.; Meijer, E. W. *J. Am. Chem. Soc.* **1996**, 118, 7398.

(10) (a) Launay, N.; Caminade, A.M.; Lahana, R.; Majoral, J.P. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1589.

(b) Galliot C.; Prévoté D.; Caminade A.M.; Majoral J.P. *J. Am. Chem. Soc.* **1995**, *117*, 5470.

(c) Launay N.; Caminade A.M.; Majoral J.P. *J. Organomet. Chem.* (in press).

(11)  (a) Launay, N.; Caminade, A.M.; Majoral, J.P. *J. Am. Chem. Soc.* **1995**, *117*, 3282.

(b) Slany, M.; Bardaji, M.; Casanove, M. J.; Caminade, A.M.; Majoral, J.P.; Chaudret, B. *J. Am. Chem. Soc.* **1995**, *117*, 9764.

(c) Launay, N.; Slany, M.; Caminade, A.M.; Majoral, J.P. *J. Org. Chem.* **1996**, *61*, 3799.

(d) Lartigue, M.L.; Slany, M.; Caminade, A.M.; Majoral, J.P. *Chem. Eur. J.* **1996**, *2*, 1417.

(e) Slany, M.; Caminade, A.M.; Majoral, J.P. *Tetrahedron Lett.* **1996**, *37*, 9053.

(f) Majoral J.P; Caminade A.M. *Actu. Chim.* **1996**, 13.

(g) Bardaji, M.; Kustos, M.; Caminade, A.M.; Majoral, J.P.; Chaudret, B. *Organometallics* **1997**, *16*, 403.

(h) Slany M.; Bardaji M.; Caminade A.M.; Chaudret B.; Majoral J.P. *Inorg. Chem.* **1997**, *36*, 1939.

(12)  For reviews on the Horner-Wadsworth-Emmons reaction see for example (a) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87.

(b) Maryanoff, B.E.; Reitz, A.B. *Chem. Rev.* **1989**, *89*, 863.

(13)  Le Roy-Gourvennec, S.; Masson, S. *Synthesis*, **1995**, 1393.

(14)  Lartigue, M.L.; Caminade, A.M.; Majoral, J.P. (to be published)

## Acknowledgements

**Table 1:**

| 3 | Yield % | $^{31}$P NMR $\delta$ (THF) | $^1$H NMR $\delta$, $J$ (Hz) | $^{13}$C $\{^1$H$\}$ NMR, $\delta$, $J$ (Hz) |
|---|---|---|---|---|
| a-[$G_1$] | 35 | 51.6 ($P_0$), 60.9 ($P_1$) | $^a$ 1.31 (t, $J$ = 7.0, 18H, CH$_2$-C$\underline{\text{H}}_3$), 3.37 (d, $J$ = 10.5, 9H, P$_1$-N-C$\underline{\text{H}}_3$), 4.24 (q, $J$ = 7.0, 12H, C$\underline{\text{H}}_2$-CH$_3$), 6.34 (d, $J$ = 16.0, 6H, CH=C$\underline{\text{H}}$-CO), 7.22 (d, $J$ = 8.1, 12H, $C_1^2$H), 7.29 (d, $J$ = 8.3, 6H, $C_0^2$H), 7.47 (d, $J$ = 8.0, 12H, $C_1^3$H), 7.49 (d, $J$ = 8.1, 6H, $C_0^2$H), 7.61 (d, $J$ = 16.0, 6H, C$\underline{\text{H}}$=CH-CO), 7.72 (s, 3H, CH=N) | $^a$ 14.3 (s, CH$_2$-$\underline{\text{C}}$H$_3$), 33.0 (d, $J$ = 14, P$_1$-N-CH$_3$), 60.5 (s, $\underline{\text{C}}$H$_2$-CH$_3$), 118.4 (s, CH=$\underline{\text{C}}$H-CO), 121.5 (d, $J$ = 4, $C_0^2$), 121.9 (d, $J$ = 4, $C_1^2$), 128.5 (s, $C_0^3$), 129.4 (s, $C_1^3$), 131.9 (s, $C_1^4$), 132.6 (s, $C_0^4$), 138.8 (d, $J$ = 14, CH=CH-CO), 143.3 (s, $\underline{\text{C}}$H=N), 151.2 (d, $J$ = 8, $C_0^1$), 151.9 (d, $J$ = 6, $C_1^1$), 166.8 (s, C=O) |
| a-[$G_4$] | 20 | 51.7 ($P_0$), 61.0 ($P_4$), 61.6 ($P_3$), 62.0 ($P_2$), 62.3 ($P_1$) | $^a$ 1.25 (m, 144H, CH$_2$-C$\underline{\text{H}}_3$), 3.30 (d, $J$ = 8.6, 135H, P$_{1\text{-}4}$-N-CH$_3$), 4.17 (m, 96H, C$\underline{\text{H}}_2$-CH$_3$), 6.30 (d, $J$ = 15.9, 48H, CH=C$\underline{\text{H}}$-CO), 7.00-7.60 (m, 465H, C$_6$H$_4$, CH=N, C$\underline{\text{H}}$=CH-CO) | $^a$ 14.1 (s, CH$_2$-$\underline{\text{C}}$H$_3$), 32.8 (d, $J$ = 13, P$_{1\text{-}4}$-N-CH$_3$), 60.4 (s, $\underline{\text{C}}$H$_2$-CH$_3$), 118.1 (s, CH=$\underline{\text{C}}$H-CO), 121.7 (d, $J$ = 4, $C_0^2$, $C_1^2$, $C_2^2$, $C_3^2$, $C_4^2$), 128.1 (br s, $C_0^3$, $C_1^3$, $C_2^3$, $C_3^3$), 129.2 (s, $C_4^3$), 131.6 (br s, $C_4^4$), 131.8 (br s, $C_0^4$, $C_1^4$, $C_2^4$, $C_3^4$), 138.5-139.0 (m, CH=N), 143.1 (s, $\underline{\text{C}}$H=CH-CO), 150.5-150.7 (m, $C_0^1$, $C_1^1$, $C_2^1$), 151.3 (d, $J$ = 8, $C_3^1$), 151.7 (d, $J$ = 8, $C_4^1$), 166.6 (s, C=O) |
| b-[$G_1$] | 35 | 18.1 (P(O)), 51.7 ($P_0$), 61.1 ($P_1$) | $^a$ 1.31 (t, $J$ = 7.1, 36H, CH$_2$-C$\underline{\text{H}}_3$), 3.35 (d, $J$ = 10.6, 9H, P$_1$-N-C$\underline{\text{H}}_3$), 4.01-4.16 (m, 24H, C$\underline{\text{H}}_2$-CH$_3$), 6.15 (dd, $J$ = 17.3, 6H, CH=C$\underline{\text{H}}$-P(O)), 7.18-7.77 (m, 39H, C$_6$H$_4$, CH=$\underline{\text{N}}$), 7.47 (d, $J$ = 17.3, 6H, C$\underline{\text{H}}$=CH-P(O)) | $^a$ 16.2 (d, $J$ = 7, CH$_2$-$\underline{\text{C}}$H$_3$), 32.9 (d, $J$ = 13, P$_1$-N-CH$_3$), 61.7 (d, $J$ = 5, $\underline{\text{C}}$H$_2$-CH$_3$), 113.9 (d, $J$ = 191, CH=$\underline{\text{C}}$H-P(O)), 121.4 (d, $J$ = 4, $C_0^2$), 121.7 (d, $J$ = 5, $C_1^2$), 128.3 (s, $C_0^3$), 128.9 (s, $C_1^3$), 131.8 (s, $C_0^4$), 132.3 (d, $J$ = 4, $C_1^4$), 138.7 (d, $J$ = 14, CH=N), 147.3 (d, $J$ = 7, $\underline{\text{C}}$H=CH-P(O)), 151.0 (d, $J$ = 7, $C_0^1$), 151.6 (d, $J$ = 7, $C_1^1$) |

# Table 1 (*Continued*):

| | | | | |
|---|---|---|---|---|
| b-[G$_4$] | 37 | 18.1 (P(O)), 51.7 (P$_0$), 61.2 (P$_4$), 61.6 (P$_3$), 61.7 (br s, P$_2$, P$_1$) | $^a$ 1.30 (t, $J$ = 6.8, 288H, CH$_2$-$\underline{C}$H$_3$), 3.31 (br d, $J$ = 8.4, 135H, P$_{1-4}$-N-CH$_3$), 4.00-4.10 (m, 192H, $\underline{C}$H$_2$-CH$_3$), 6.13 (dd, $J$ = $J$ = 17.5, 48H, CH=$\underline{C}$H-P(O)), 7.19-7.67 (m, 465H, C$_6$H$_4$, CH=N, $\underline{C}$H=CH-P(O)) | $^a$ 16.2 (d, $J$ = 7, CH$_2$-$\underline{C}$H$_3$), 32.8 (br d, $J$ = 13, P$_{1-4}$-N-CH$_3$), 61.7 (d, $J$ = 5, $\underline{C}$H$_2$-CH$_3$), 113.9 (d, $J$ = 192, CH=$\underline{C}$H-P(O)), 121.7 (br d, $J$ = 4, C$_0^2$, C$_1^2$, C$_2^2$, C$_3^2$, C$_4^2$), 128.2 (br s, C$_0^3$, C$_1^3$, C$_2^3$, C$_3^3$), 128.9 (s, C$_4^3$), 131.8 (d, $J$ = 4, C$_4^4$), 132.3 (br s, C$_0^4$, C$_1^4$, C$_2^4$, C$_3^4$), 139.0 (br d, $J$ = 14, CH=N), 147.3 (d, $J$ = 5, $\underline{C}$H=CH-P(O)). 151.2 (br d, $J$ = 6, C$_0^1$, C$_1^1$, C$_2^1$, C$_3^1$), 151.6 (d, $J$ = 7, C$_4^1$) |
| c-[G$_1$] | 25 | 51.6 (P$_0$), 61.4 (P$_1$) | $^a$ 1.72 (br s, 36H, N-CH$_2$-($\underline{C}$H$_2$)$_3$), 3.35 (d, $J$ = 10.6, 9H, P$_1$-N-CH$_3$), 3.73 (br s, 12H, N-CH$_2$), 4.28 (br s, 12H, N-CH$_2$), 6.20 (d, $J$ = 12.0, (6*0.1)H, CH=$\underline{C}$H-C(S)$^Z$), 6.26 (d, $J$ = 12.0, (6*0.1)H, $\underline{C}$H=CH-C(S)$^Z$), 7.14 (d, $J$ = 15.0, (6*0.9)H, CH=$\underline{C}$H-C(S)$^E$), 7.50 (d, $J$ = 15.3, (6*0.9)H, $\underline{C}$H=CH-C(S)$^E$), 7.11-7.75 (m, 39H, C$_6$H$_4$, CH=N) | $^a$ 24.0, 24.6, 25.3 [3s, N-CH$_2$-($\underline{C}$H$_2$)$_3$], 32.9 (d, $J$ = 13, P$_1$-N-CH$_3$), 51.5 (s, N-CH$_2$), 51.6 (s, N-CH$_2$), 121.4 (d, $J$ = 4, C$_0^2$), 121.6 (d, $J$ = 5, C$_1^2$), 124.9 (s, CH=$\underline{C}$H-C(S)$^Z$), 126.0 (s, CH=$\underline{C}$H-C(S)$^Z$), 128.0 (s, C$_0^3$), $\underline{C}$H=CH-C(S)$^E$), 128.3 (s, C$_0^3$), $\underline{C}$H=CH-C(S)$^Z$), 128.6 (s, C$_1^3$), 132.4 (s, C$_0^4$), 132.8 (s, C$_1^4$), 138.5 (d, $J$ = 14, CH=N), 140.4 (s, $\underline{C}$H=CH-C(S)$^E$), 150.9 (d, $J$ = 7, C$_1^1$), 151.0 (d, $J$ = 9, C$_0^1$), 193.9 (s, C=S$^Z$), 194.6 (s, C=S$^Z$) |
| c-[G$_4$] | 25 | 51.6 (P$_0$), 61.4 (P$_4$), 61.8 (br s, P$_1$, P$_2$, P$_3$) | $^a$ 1.65 (br s, 288H, N-CH$_2$-($\underline{C}$H$_2$)$_3$), 3.28 (d, $J$ = 8.9, 135H, P$_{1-4}$-N-CH$_3$), 3.73 (br s, 96H, N-CH$_2$), 4.20 (br s, 96H, N-CH$_2$), 6.20 (br s, (96*0.1)H, CH=CH-C(S), $\underline{C}$H=CH-C(S)$^Z$), 6.91- 7.65 (m, 369H, C$_6$H$_4$, CH=N), 6.94 (d, $J$ = 15.0, (48*0.9)H, CH=$\underline{C}$H-C(S)$^E$), 7.45 (d, $J$ = 15.0, (48*0.9)H, $\underline{C}$H=CH-C(S)$^E$) | $^a$ 24.2, 25.4, 26.8 [3s, N-CH$_2$-($\underline{C}$H$_2$)$_3$], 32.9 (m, P$_{1-4}$-N-CH$_3$), 51.6 (s, N-CH$_2$), 51.8 (s, N-CH$_2$), 121.7 (br s, C$_0^2$, C$_1^2$, C$_2^2$, C$_3^2$, C$_4^2$), 126.1 (s, CH=$\underline{C}$H-C(S)$^Z$), 125.5 (s, CH=$\underline{C}$H-C(S)$^Z$), 128.3 (br s, C$_0^3$, C$_1^3$, C$_2^3$, C$_3^3$), 128.8 (s, C$_4^3$), 129.0 (s, C(S)$^E$), 128.3 (br s, C$_0^3$, C$_1^3$, C$_2^3$, C$_3^3$), 132.1 (br s, C$_0^4$, C$_1^4$, C$_2^4$, C$_3^4$), 132.9 (s, $\underline{C}$H=CH-C(S)$^Z$), 138.9-139.2 (m, $\underline{C}$H=N), 140.6 (s, $\underline{C}$H=CH-C(S)$^E$), 151.0 (d, $J$ = 7, C$_4^1$), 151.3 (d, $J$ = 6, C$_0^1$, C$_1^1$, C$_2^1$, C$_3^1$), 193.9 (s, C=S$^Z$), 194.6 (s, C=S$^E$) |

**Table 1** *(Continued)*:

| | | | $^{b}$ $^1$H NMR | $^{b}$ $^{13}$C NMR |
|---|---|---|---|---|
| **d-[G$_1$]** | 20 | 51.6 (P$_0$), 61.0 (P$_1$) | 3.22 (d, $J = 4.5$, 18H, NH-C$\underline{H}_3$), 3.46 (d, $J = 10.6$, 9H, P$_1$-N-C$\underline{H}_3$), 6.29 (d, $J = 12.3$, (6*0.3)H, CH=C$\underline{H}$-C(S)$^Z$), 6.34 (d, $J = 12.3$, (6*0.3)H, C$\underline{H}$=CH-C(S)$^Z$), 6.91 (d, $J = 15.3$, (6*0.7)H, C$\underline{H}$=CH-C(S)$^E$), 7.23 (d, $J = 8.5$, 6H, C$_0^2$H), 7.43 (d, $J = 8.1$, 12H, C$_1^2$H), 7.60 (d, $J = 8.1$, 12H, C$_1^3$H), 7.78 (d, $J = 15.3$, (6*0.7)H, CH=C$\underline{H}$-C(S)$^E$), 7.88 (d, $J = 8.7$, 6H, C$_0^3$H), 7.90 (s, 3H, CH=N), 9.20 (m, (6*0.3)H, NH$^Z$), 9.33 (m, (6*0.7)H, NH$^E$) | 34.0 (s, NH-$\underline{C}$H$_3$), 34.5 (d, $J = 13$, P$_1$-N-$\underline{C}$H$_3$), 123.5 (d, $J = 4$, C$_0^2$), 123.8 (d, $J = 3$, C$_1^2$), 128.0 (s, CH=$\underline{C}$H-C(S)$^Z$), 130.4 (s, C$_0^3$), 130.9 (s, C$_1^3$), 132.0 (s, CH=$\underline{C}$H-C(S)$^E$), 134.0 (s, $\underline{C}$H=CH-C(S)$^Z$), 135.0 (s, C$_1^4$), 135.3 (s, C$_0^4$), 140.6 (s, $\underline{C}$H=CH-C(S)$^E$), 141.5 (d, $J = 12$, CH=N), 152.2 (d, $J = 7$, C$_0^1$), 153.4 (d, $J = 8$, C$_1^1$), 196.8 (s, C=S$^Z$), 199.3 (s, C=S$^E$) |
| **d-[G$_3$]** | 20 | 51.6 (P$_0$), 60.9 (P$_3$), 61.4 (br s, P$_1$, P$_2$) | 3.30 (d, $J = 4.4$, 72H, NH-C$\underline{H}_3$), 3.52 (d, $J = 9.9$, 63H, P$_{1\text{-}3}$-N-C$\underline{H}_3$), 6.36 (d, $J = 12.8$, (24*0.5)H, CH=C$\underline{H}$-C(S)$^Z$), 6.43 (d, $J = 12.8$, (24*0.5)H, C$\underline{H}$=CH-C(S)$^Z$), 6.91-8.00 (m, 201H, C$_6$H$_4$, CH=N), 6.99 (d, $J = 15.5$, (24*0.5)H, C$\underline{H}$=CH-C(S)$^E$), 7.72 (d, $J = 15.5$, (24*0.5)H, CH=C$\underline{H}$-C(S)$^E$), 9.23 m, (24*0.5)H, NH$^Z$), 9.33 (m, (24*0.5)H, NH$^E$) | 34.0 (s, NH-$\underline{C}$H$_3$), 34.4 (d, $J = 13$, P$_{1\text{-}3}$-N-CH$_3$), 123.1 (br s, C$_0^2$, C$_1^2$, C$_2^2$), 123.8 (br s, C$_3^2$), 128.0 (s, CH=$\underline{C}$H-C(S)$^Z$), 129.4 (s, C$_2^3$), 130.2 (br s, C$_0^3$, C$_1^3$), 130.9 (s, C$_3^3$), 131.9 (s, CH=$\underline{C}$H-C(S)$^E$), 134.0 (s, $\underline{C}$H=CH-C(S)$^Z$), 134.6 (s, C$_3^4$), 135.0 (br s, C$_0^4$, C$_1^4$, C$_2^4$), 140.6 (s, $\underline{C}$H=CH-C(S)$^E$), 141.3-141.9 (m, CH=N), 153.6 (d, $J = 5$, C$_0^1$, C$_1^1$, C$_2^1$, C$_3^1$), 196.9 (s, C=S$^Z$), 199.3 (s, C=S$^E$) |
| **e-[G$_1$]** | 15 | 51.6 (P$_0$), 61.0 (P$_1$) | 3.53 (d, $J = 10.7$, 9H, P$_1$-N-C$\underline{H}_3$), 6.56 (d, $J = 16.0$, 6H, CH=C$\underline{H}$-CO), 7.41 (d, $J = 7.4$, 12H, C$_1^2$H), 7.49 (d, $J = 8.5$, 6H, C$_0^2$H), 7.74 (d, $J = 8.6$, 12H, C$_1^3$H), 7.74 (d, $J = 16.0$, 6H, C$\underline{H}$=CH-CO), 7.95 (d, $J = 8.6$, 6H, C$_0^3$H), 7.98 (s, 3H, CH=N), 8.50 (br s, 6H, OH) | 32.9 (d, $J = 13$, P$_1$-N-$\underline{C}$H$_3$), 119.3 (s, CH=$\underline{C}$H-CO), 121.9 (d, $J = 4$, C$_0^2$), 122.2 (d, $J = 5$, C$_1^2$), 128.8 (s, C$_0^3$), 129.8 (s, C$_1^3$), 132.7 (s, C$_1^4$), 133.6 (s, C$_0^4$), 139.9 (d, $J = 14$, CH=N), 143.4 (s, $\underline{C}$H=CH-CO), 151.8 (d, $J = 7$, C$_0^1$), 152.5 (d, $J = 8$, C$_1^1$), 167.4 (s, CO) |

**Table 1 (*Continued*):**

| | | | | |
|---|---|---|---|---|
| e-[G$_3$] | 15 | 51.8 (P$_0$), 61.0 (P$_3$), 61.5 (P$_2$), 61.9 (P$_1$) | b 3.53 (d, $J$ = 10.2, 63H, P$_{1-3}$-N-CH$_3$), 6.60 (d, $J$ = 16.0, 24H, CH=C<u>H</u>-CO), 7.25-7.96 (m, 201H, C$_6$H$_4$, CH=N, O<u>H</u>), 7.77 (d, $J$ = 16.0, 24H, C<u>H</u>=CH-CO) | b 32.9 (d, $J$ = 13, P$_{1-3}$-N-CH$_3$), 119.3 (s, CH=<u>C</u>H-CO), (d, $J$ = 4, C$_0^2$, C$_1^2$, C$_2^2$, C$_3^2$), 128.5 (s, C$_0^3$), 128.6 (br s, C$_1^3$, C$_3^2$), 129.8 (s, C$_3^3$), 132.6 (s, C$_3^4$), 133.1 (s, C$_1^4$), 133.6 (s, C$_0^4$), 140.2 (d, $J$ = 13, CH=N), 143.5 (s, <u>C</u>H=CH-CO), 152.1 (d, $J$ = 6, C$_0^1$, C$_1^1$, C$_2^1$), 152.5 (d, $J$ = 7, C$_3^1$), 167.4 (s, CO) |
| f-[G$_1$] | 25 | 51.6 (P$_0$), 61.0 (P$_1$) | b 3.52 (d, $J$ = 10.7, 9H, P$_1$-N-CH$_3$), 4.43 (d, $J$ = 5.5, 12H, N-CH$_2$), 4.60 (d, $J$ = 4.8, 12H, N-CH$_2$), 6.35 (d, $J$ = 12.5, (6*0.1)H, CH=C<u>H</u>-C(S)$^Z$), 6.44 (d, $J$ = 12.5, (6*0.1)H, C<u>H</u>=CH-C(S)$^Z$), 7.17 (d, $J$ = 15.0, (6*0.9)H, CH=C<u>H</u>-C(S)$^E$), 7.38 (d, $J$ = 7.7, 12H, C$_1^2$H), 7.48 (d, $J$ = 7.9, 6H, C$_0^2$H), 7.69 (d, $J$ = 8.4, 12H, C$_1^3$H), 7.90 (d, $J$ = 7.7, 6H, C<u>H</u>=CH-C(S)$^E$), 7.95 (d, $J$ = 7.7, 6H, CH=N, OH), 9.24 (br s, (6*0.9)H, C$_0^3$H), 7.93 (br s, 9H, CH=N, OH), 9.24 (br s, (6*0.9)H, NH$^E$), 9.49 (br s, (6*0.1)H, NH$^Z$) | b 32.9 (d, $J$ = 12, P$_1$-N-CH$_3$), 47.2 (s, N-CH$_2$), 121.9 (d, $J$ = 5, C$_0^2$), 122.2 (d, $J$ = 4, C$_1^2$), 127.3 (s, CH=<u>C</u>H-C(S)$^Z$), 128.1 (s, CH=<u>C</u>H-C(S)$^E$), 128.9 (s, C$_0^3$), 129.5 (s, C$_1^3$), 131.7 (s, CH=<u>C</u>H-C(S)$^Z$), 133.5 (s, C$_1^4$), 133.7 (s, C$_0^4$), 139.9 (d, $J$ = 13, CH=N), 140.4 (s, <u>C</u>H=CH-C(S)$^E$), 151.9 (d, $J$ = 9, C$_0^1$), 152.1 (d, $J$ = 10, C$_1^1$), 170.3 (s, CO), 195.3 (s, C=S$^E$), 196.7 (s, C=S$^Z$) |
| f-[G$_4$] | 10 | 51.7 (P$_0$), 61.0 (P$_4$), 61.2 (P$_1$, P$_2$), 61.6 (P$_3$) | b 3.46 (m, 135H, P$_{1-4}$-N-CH$_3$), 4.42 (d, $J$ = 4.2, 96H, N-CH$_2$), 4.60 (d, $J$ = 4.2, 96H, N-CH$_2$), 6.33 (d, $J$ = 12.5, (48*0.35)H, CH=CH-C(S)$^Z$), 6.41 (d, $J$ = 12.5, (48*0.35)H, CH=CH-C(S)$^Z$), 7.14 (d, $J$ = 15.2, (48*0.65)H, C<u>H</u>=CH-C(S)$^E$), 7.00-7.90 (m, 465H+(48*0.65)H, C$_6$H$_4$, CH=N, C<u>H</u>=CH-C(S)$^E$, OH), 9.26 (br s, (48*0.65)H, NH$^E$), 9.49 (br s, (48*0.35)H, NH$^Z$) | b 32.9 (m, P$_{1-4}$-N-CH$_3$), 46.5 (br s, N-CH$_2$), 121.6 (br s, C$_0^2$, C$_1^2$, C$_2^2$), 121.9 (br s, C$_3^2$), 122.2 (br s, C$_4^2$), 127.4 (s, CH=<u>C</u>H-C(S)$^Z$), 128.6 (m, C$_0^3$, C$_1^3$, C$_2^3$, C$_3^3$), 129.5 (br s, C$_4^3$), 131.6 (s, <u>C</u>H=CH-C(S)$^Z$), 133.0 (br s, C$_0^4$, C$_1^4$, C$_2^4$, C$_3^4$, C$_4^4$), 140.5 (m, CH=N, <u>C</u>H=CH-C(S)$^E$), 150.7 (br s, C$_0^1$, C$_1^1$, C$_2^1$, C$_3^1$), 152.0 (d, $J$ = 6, C$_4^1$), 170.0 (s, CO), 197.5 (s, C=S$^E$), 198.4 (s, C=S$^Z$) |

**Table 1** (*Continued*):

| | | | $^1$H NMR | $^{13}$C NMR |
|---|---|---|---|---|
| **g-[G$_1$]** | 43 | 51.6 (P$_0$), 61.3 (P$_1$) | $b$ 1.44 (d, $J$ = 7.2, 18H, CH-C$\underline{H}_3$), 3.36 (d, $J$ = 8.6, 9H, P$_1$-N-CH$_3$), 5.24 (m, 6H, C$\underline{H}$-CH$_3$), 6.17 (d, $J$ = 12.3, (6*0.1)H, CH=C$\underline{H}$-C(S)$^Z$), 6.26 (d, $J$ = 12.3, (6*0.1)H, CH=C$\underline{H}$-C(S)$^Z$), 6.72-7.83 (m, 45H, C$_6$H$_4$, CH=N, OH), 6.97 (d, $J$ = 15.3, (6*0.9)H, C$\underline{H}$=CH-C(S)$^E$), 7.75 (d, $J$ = 15.3, (6*0.9)H, C$\underline{H}$=CH-C(S)$^E$), 9.17 (d, $J$ = 7.4, (6*0.9)H, NH$^E$), 9.35 (d, $J$ = 7.4, (6*0.1)H, NH$^Z$) | $b$ 17.2 (s, CH-$\underline{C}$H$_3$), 33.4 (d, $J$ = 13, P$_1$-N-CH$_3$), 54.4 (s, CH), 122.0 (d, $J$ = 4, C$_0$$^2$), 122.4 (d, $J$ = 5, C$_1$$^2$), 128.2 (s, CH=$\underline{C}$H-C(S)$^Z$), 128.4 (s, CH=$\underline{C}$H-C(S)$^E$), 129.3 (s, C$_0$$^3$), 129.9 (s, C$_1$$^3$), 131.9 (s, $\underline{C}$H=CH-C(S)$^Z$), 133.7 (s, C$_1$$^4$), 134.0 (s, C$_0$$^4$), 140.7 (d, $J$ = 13, CH=N), 141.1 (s, $\underline{C}$H=CH-C(S)$^E$), 151.9 (d, $J$ = 7, C$_0$$^1$), 152.3 (d, $J$ = 8, C$_1$$^1$), 174.6 (s, CO), 194.9 (s, C=S$^E$), 198.0 (s, C=S$^Z$) |
| **g-[G$_3$]** | 40 | 51.9 (P$_0$), 60.6-61.7 (m, P$_1$, P$_2$, P$_3$) | $b$ 1.61 (d, $J$ = 7.0, 72H, CH-C$\underline{H}_3$), 3.50 (d, $J$ = 9.6, 63H, P$_{1-3}$-N-CH$_3$), 5.41 (m, 24H, C$\underline{H}$-CH$_3$), 6.32 (d, $J$ = 12.6, (24*0.15)H, CH=C$\underline{H}$-C(S)$^Z$), 6.42 (d, $J$ = 12.6, (24*0.15)H, CH=C$\underline{H}$-C(S)$^Z$), 7.04-7.96 (m, 225H, C$_6$H$_4$, CH=N, OH), 7.11 (d, $J$ = 15.3, (24*0.85)H, CH=CH-C(S)$^E$), 7.90 (d, $J$ = 15.3, (24*0.85)H, C$\underline{H}$=CH-C(S)$^E$), 9.30 (d, $J$ = 6.6, (24*0.85)H, NH$^E$), 9.45 (d, $J$ = 7.3, (24*0.15)H, NH$^Z$) | $b$ 17.2 (s, CH-$\underline{C}$H$_3$), 33.0 (br d, $J$ = 12, P$_{1-3}$-N-CH$_3$), 53.7 (br s, CH), 122.3 (d, $J$ = 5, C$_0$$^2$, C$_1$$^2$, C$_2$$^2$, C$_3$$^2$), 127.2 (s, CH=$\underline{C}$H-C(S)$^Z$), 128.3 (s, CH=$\underline{C}$H-C(S)$^E$), 128.8 (br s, C$_0$$^3$, C$_1$$^3$, C$_2$$^3$), 129.6 (s, C$_3$$^3$), 131.9 (s, $\underline{C}$H=CH-C(S)$^Z$), 133.2 (br s, C$_0$$^4$, C$_1$$^4$, C$_2$$^4$), 133.5 (br s, C$_3$$^4$), 139.9-140.5 (m, CH=N), 140.8 (s, $\underline{C}$H=CH-C(S)$^E$), 150.9 (d, $J$ = 6, C$_0$$^1$), 151.9 (d, $J$ = 8, C$_1$$^1$, C$_2$$^1$), 152.3 (d, $J$ = 6, C$_3$$^1$), 173.7 (br s, CO), 194.7 (s, C=S$^E$), 197.5 (s, C=S$^Z$) |
| **h-[G$_1$]** | 20 | 51.6 (P$_0$), 61.0 (P$_1$) | $b$ 3.30-3.37 (m, 12H, C$\underline{H}_2$Ph), 3.51 (d, $J$ = 10.6, 9H, P$_1$-N-CH$_3$), 5.56 (m, 6H, CH), 6.28 (d, $J$ = 12.2, (6*0.1)H, CH=CH-C(S)$^Z$), 6.38 (d, $J$ = 15.3, (6*0.1) H, CH=CH-C(S)$^Z$), 7.17 (d, $J$ = 15.3, (6*0.9)H, CH=CH-C(S)$^E$), 7.92 (d, $J$ = 15.3, (6*0.9)H, C$\underline{H}$=CH-C(S)$^Z$), 7.04-7.97 (m, 45H, C$_6$H$_4$, CH=N, OH), 9.20 (br s, (6*0.9)H, NH$^E$), 9.40 (br s, (6*0.1)H, NH$^Z$) | $b$ 32.9 (d, $J$ = 13, P$_1$-N-CH$_3$), 36.5 (s, $\underline{C}$H$_2$Ph), 59.4 (s, $\underline{C}$H$_2$Ph), CO), 121.9 (d, $J$ = 4, C$_0$$^2$), 122.2 (d, $J$ = 5, C$_1$$^2$), 126.9 (s, C$_1$$^2$), 127.1 (s, CH=$\underline{C}$H-C(S)$^Z$), 128.3 (s, C$_0$$^3$), 128.5 (s, C$_1$$^3$), 128.8 (s, p-C$_6$H$_5$), 129.5 (s, o-C$_6$H$_5$), 129.9 (s, m-C$_6$H$_5$), 131.6 (s, $\underline{C}$H=CH-C(S)$^Z$), 133.6 (s, C$_1$$^4$), 133.7 (s, C$_0$$^4$), 137.8 (s, i-C$_6$H$_5$), 139.9 (d, $J$ = 12, CH=N), 140.7 (s, C$_0$$^4$), $\underline{C}$H=CH-C(S)$^E$), 151.9 (d, $J$ = 8, C$_0$$^1$), 152.1 (d, $J$ = 6, C$_1$$^1$), 173.2 (s, CO), 194.6 (s, C=S$^E$), 198.0 (s, C=S$^Z$) |

**Table 1** *(Continued):*

| | | | | |
|---|---|---|---|---|
| **h-[G$_4$]** | 10 | 51.6 (P$_0$), 61.4 (P$_4$), 61.9 (br s, P$_1$, P$_2$, P$_3$) | $b$ 3.20-3.54 (m, 231H, C$\underline{H}_2$Ph, P$_{1-4}$-N-C$\underline{H}_3$), 5.70 (m, 48H, CH), 6.26 (d, $J$ = 12.0, (48*0.35)H, CH=C$\underline{H}$-C(S)$^Z$), 6.36 (d, $J$ = 12.0, (48*0.35)H, C$\underline{H}$=CH-C(S)$^Z$), 7.00-7.94 (m, 657H+(96*0.65)H, C$_6$H$_4$, CH=N, OH, CH=C$\underline{H}$-C(S)$^E$, C$\underline{H}$=CH-C(S)$^E$, 9.14 (br s, (48*0.65)H, NH$^E$), 9.50 (br s, (48*0.35)H, NH$^Z$) | $b$ 32.9 (d, $J$ = 14, P$_{1-4}$-N-C$\underline{H}_3$), 36.5 (br s, C$\underline{H}_2$Ph), 58.9 (s, C$\underline{H}$-CO), 121.6 (br s, C$_0^2$, C$_1^2$), 122.2 (br s, C$_2^2$, C$_3^2$, C$_4^2$), 127.0 (s, CH=C$\underline{H}$-C(S)$^E$), 127.9 (s, CH=C$\underline{H}$-C(S)$^Z$), 128.6 (br s, C$_0^3$, C$_1^3$, C$_2^3$, C$_3^3$, C$_4^3$, $p$-C$_6$H$_5$), 129.5 (s, $o$-C$_6$H$_5$), 129.9 (s, C$_0^3$, C$_1^3$, C$_2^3$, C$_3^3$, C$_4^3$, $p$-C$_6$H$_5$), 129.5 (s, $o$-C$_6$H$_5$), 129.9 (s, $m$-C$_6$H$_5$), 131.5 (s, C$\underline{H}$=CH-C(S)$^Z$), 133.0 (br s, C$_0^4$, C$_1^4$, C$_2^4$, C$_3^4$, C$_4^4$), 137.4 (s, $i$-C$_6$H$_5$), 138.5-142.8 (m, CH=N, C$\underline{H}$=CH-C(S)$^E$), 150.6 (m, C$_0^1$, C$_1^1$, C$_2^1$, C$_3^1$), 152.0 (d, $J$ = 7, C$_4^1$), 194.8 (s, C=S$^E$), 196.0 (s, C=S$^Z$) |
| **i-[G$_1$]** | 15 | 51.6 (P$_0$), 61.0 (P$_1$) | $b$ 2.17 (s, 18H, SCH$_3$), 2.10-2.51 (2m, 12H, CH-C$\underline{H}_2$), 2.70 (t, $J$ = 7.5, 12H, CH$_2$S), 3.53 (d, $J$ = 10.6, 9H, P$_1$-N-CH$_3$), 5.55 (m, 6H, C$\underline{H}$-CH$_2$), 6.35 (d, $J$ = 12.0, (6*0.1)H, CH=C$\underline{H}$-C(S)$^Z$), 6.43 (d, $J$ = 12.5, (6*0.1)H, C$\underline{H}$=CH-C(S)$^Z$), 7.15 (d, $J$ = 15.0, (6*0.9) H, CH=C$\underline{H}$-C(S)$^E$), 7.38 (d, $J$ = 7.9, 12H, C$_1^2$H), 7.48 (d, $J$ = 8.0, 6H, C$_0^2$H), 7.68 (d, $J$ = 7.8, 12H, C$_1^3$H), 7.90 (d, $J$ = 15.0, (6*0.9)H, C$\underline{H}$=CH-C(S)$^E$), 7.95 (d, $J$ = 7.6, 6H, C$_0^3$H), 7.88 (br s, 9H, CH=N, OH), 9.34 (d, $J$ = 5.6, (6*0.9)H, NH$^E$), 9.52 (d, $J$ = 6.4, (6*0.1)H, NH$^Z$) | $b$ 14.9 (s, SCH$_3$), 30.5 (s, C$\underline{H}_2$S), 32.0 (s, CH-C$\underline{H}_2$), 32.9 (d, $J$ = 12, P$_1$-N-CH$_3$), 57.6 (s, C$\underline{H}$-CH$_2$), 121.9 (d, $J$ = 4, C$_0^2$), 122.2 (d, $J$ = 5, C$_1^2$), 126.9 (s, CH=C$\underline{H}$-C(S)$^Z$), 128.3 (s, CH=C$\underline{H}$-C(S)$^E$), 128.9 (s, C$_0^3$), 129.5 (s, C$_1^3$), 131.7 (s, CH=C$\underline{H}$-C(S)$^Z$), 133.5 (s, C$_1^4$), 133.7 (s, C$_0^4$), 140.0 (d, $J$ = 13, CH=N), 140.7 (s, C$\underline{H}$=CH-C(S)$^E$), 151.8 (d, $J$ = 8, C$_0^1$), 152.1 (d, $J$ = 7, C$_1^1$), 173.2 (br s, CO), 195.1 (s, C=S$^E$), 198.5 (s, C=S$^Z$) |

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**Table 1 (*Continued*):**

| i-[G$_4$] | 10 | 51.6 (P$_0$), 61.0 (P$_4$), 61.6 (P$_1$, P$_2$, P$_3$) | *b* 2.15 (br s, 144H, S<u>C</u>H$_3$), 2.32 (m, 96H, CH-<u>C</u>H$_2$), 2.66 (m, 96H, <u>C</u>H$_2$S), 3.51 (d, J = 6.5, 135H, P$_{1-4}$-N-<u>C</u>H$_3$), 5.53 (m, 48H, <u>C</u>H-CH$_2$), 6.35 (m, (96*0.15)H, <u>C</u>H=CH-C(S)$^Z$, <u>C</u>H=CH-C(S)$^Z$), 7.04-7.86 (m, 465+(96*0.85)H, C$_6$H$_4$, CH=N, OH, CH=<u>C</u>H-C(S)$^E$, <u>C</u>H=CH-C(S)$^E$), 9.40 (br s, (48*0.85)H, NH$^E$), 9.50 (br s, (48*0.15)H, NH$^Z$) | *b* 14.9 (s, S<u>C</u>H$_3$), 30.6 (m, <u>C</u>H$_2$S), 31.0 (m, CH-<u>C</u>H$_2$), 32.9 (m, P$_{1-4}$-N-<u>C</u>H$_3$), 57.0 (m, <u>C</u>H-CH$_2$), 121.6 (m, C$_0^2$, C$_1^2$, C$_2^2$, C$_3^2$), 122.2 (br s, C$_4^2$), 127.0 (s, CH=<u>C</u>H-C(S)$^Z$), 128.6 (br s, CH=<u>C</u>H-C(S)$^E$, C$_0^3$, C$_1^3$, C$_2^3$, C$_3^3$), 129.5 (br s, C$_4^3$), 131.5 (s, CH=<u>C</u>H-C(S)$^Z$), 133.1 (br s, C$_0^4$, C$_1^4$, C$_2^4$, C$_3^4$, C$_4^4$), 140.8 (m, CH=N, <u>C</u>H=CH-C(S)$^E$), 150.7 (d, J = 7, C$_0^1$, C$_1^1$, C$_2^1$, C$_3^1$), 152.0 (br s, C$_4^1$), 168.3 (br s, CO), 195.0 (s, C=S$^E$), 198.5 (s, C=S$^Z$) |

*a* in CDCl$_3$

*b* in THF D$_8$

*Z* Z-isomers

*E* E-isomers
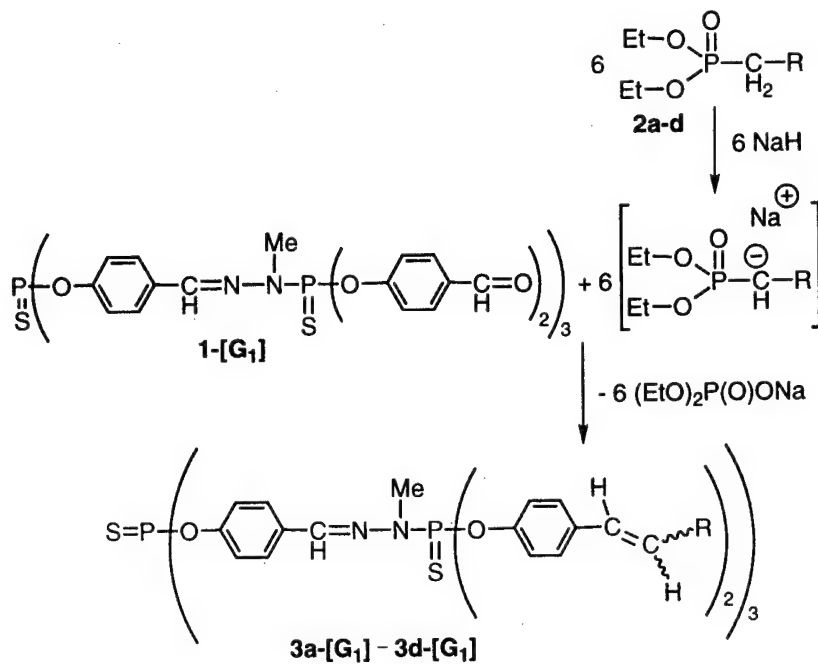
| 3 (% of *Z* isomer) | a-[G$_1$] (0) | b-[G$_1$] (0) | c-[G$_1$] (10) | d-[G$_1$] (30) |
|---|---|---|---|---|
| R | $\underset{\text{C-O-Et}}{\overset{\text{O}}{\|}}$ | $\underset{\text{O-Et}}{\overset{\overset{\text{O}}{\|}}{\underset{\text{O-Et}}{\text{P-O-Et}}}}$ | $\underset{\text{C-N}}{\overset{\text{S}}{\|}}$ piperidine | $\underset{\text{C-NHMe}}{\overset{\text{S}}{\|}}$ |
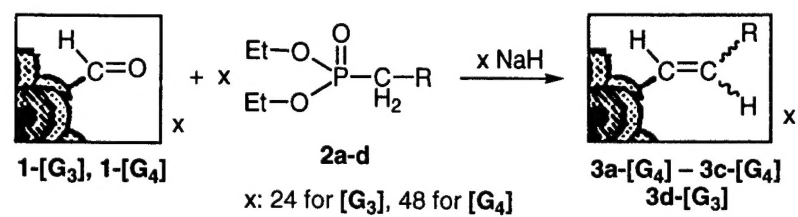
Scheme 1

| 3 (% of Z isomer) | a-[G$_4$] (0) | b-[G$_4$] (0) | c-[G$_4$] (10) | d-[G$_3$] (50) |
|---|---|---|---|---|
| R | O‖ C–O-Et | O‖ P⟨O-Et⟩⟨O-Et⟩ | S‖ C–N(piperidine) | S‖ C–NHMe |

**Scheme 2**

Scheme 3

**Numbering used for NMR:**



**Scheme 4**

**1-[G₄]**

**Figure 1**